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# CUTANEOUS PAPILLOMATOSIS

## PAPILLOMATOSE CONFLUENTE ET RÉTICULÉE

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An interesting article entitled "New Forms of Papillomatosis" was published in 1932 by Gougerot and Carteaud,[1] of France. Since the American literature contains no reference [2] to dermatoses of this kind, we believe that a report of an example of a rare dermatosis belonging in this group is warranted.

Gougerot and Carteaud pointed out that the literature concerning cutaneous papillomatoses reveals an astonishingly meager amount of information, that such eruptions are rare, that they are not generally recognized as forming a self-sustained group and that they are confused with verrucose proliferative dermatoses. They stated further that in their opinion there was a need for segregation and identification—at least from the clinical aspect—of such a group of rare dermatoses.

They described and illustrated with photographs three groups, as follows:

Group I. Punctate, pigmented, verrucous papillomatosis.
Group II. Confluent and reticulated papillomatosis.
Group III. Nummular and confluent papillomatosis.

The patient whose case is reported here exhibited an eruption which was almost a replica, both clinically and histologically, of that in one of the typical cases described by Gougerot and Carteaud under group II.

### PAPILLOMATOSE CONFLUENTE ET RÉTICULÉE

The following abstract embodies the main points of Gougerot and Carteaud's report on group II.

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1. Gougerot, H., and Carteaud, A.: New Forms of Papillomatosis, Arch. f. Dermat. u. Syph. **165**:232, 1932.

2. Except the abstract of Gougerot and Carteaud's article in The Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1932, p. 174.

Four patients were observed; two women, aged 21 and 25, and two men, aged 19 and 24, respectively. The cause of the dermatitis was unknown.

*Etiology.*—There were no concomitant warty formations or preexisting infections. It seems probable that endocrinologic disturbances, especially thyroid dysfunction, might have played a rôle in the etiology.

*Symptoms.*—This form of papillomatosis is characterized by (1) the morphologic features of individual lesions; (2) the configuration of the eruption; (3) the site of the initial manifestations and the areas of predilection; (4) the distribution of the individual lesions; (5) the concomitant manifestations (involvement of the axillae and groins).

1. Morphology of Individual Lesions: The elementary lesion consists of a papillomatous papule from 1 to 2 mm. in diameter; it is slightly elevated, round, flat topped and bright red; the surface is slightly cornified, and the borders are sharply defined. In the course of development a rapid change takes place. The red papule becomes gray, and as a result of deposit of pigment soon turns brown; the epidermis is thickened, uneven and somewhat cornified; some of the lesions are almost verrucous, resembling plane juvenile warts. The papules increase in size, attaining a diameter of from 4 to 5 mm. Further progress of the eruption results in confluence of the lesions in the form of a massed flat network which for the most part presents well defined borders. On the intermammary and epigastric regions the eruption resembles pityriasis versicolor. There is, however, absence of scaling and of infiltration. When the lesions are scratched no scales are detached but rather a kind of mealy deposit is removed.

2. Configuration of the Eruption: As the papules increase in number, they gradually merge and form a centrally situated (intermammary) diffuse, even surface, while those at the periphery spread out and form a network, which diminishes and fades as it approaches the surrounding unaffected skin.

3. Site of the Initial Lesions and Areas of Predilection: The earliest manifestations appear on the intermammary and epigastric regions.

4. Distribution of the Individual Lesions: This exhibits a definite tendency toward certain areas of predilection, namely, the intermammary and epigastric regions, where the eruption forms a rhomboid outline; the interscapular region, and the superior aspect of the shoulders (suspender areas). From these situations the eruption spreads with diminishing intensity, the involvement being upward toward the breasts and axillae, downward toward the pubes and posteriorly up and down the spine.

5. Concomitant Manifestations: These appear on the neck and in and about the axillae. The skin of the neck is thickened and the surface markings are exaggerated, roughened and pigmented, but papillomatous formations are lacking. The skin of the axillae exhibits a pronounced exaggeration of its parallel folds; the glandular orifices are prominent and enlarged and are capped with fine cornified plugs. The epidermis is grayish red or grayish brown and feels smooth to the palpating finger.

The mucosae are unaffected. Subjective symptoms are absent. The eruption undergoes an insidious and chronic evolution, new areas becoming involved at irregular intervals. The eruption is neither congenital nor hereditary.

REPORT OF A CASE

Mrs. M. S., aged 23, born in the United States of Italian parents, applied for treatment at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on April 2, 1936. She was referred by Dr. B. M. James, of Newark, N. J.

Fig. 1 (authors' case).—Confluent and reticulated papillomatosis.

The family history was irrelevant.

The patient stated that the cutaneous eruption had developed about seven years previously. Shortly after the dermatosis appeared she began to gain weight (she had gained 50 pounds [22.7 Kg.] in the past six years) and noted an increased growth of coarse hairs on the face and extremities. In 1934 a pregnancy terminated in a stillbirth at the ninth month (fetal dystocia). Since then the menses had been slightly irregular but painless. Otherwise the health had been good.

*Examination.*—The patient was dark complexioned, short and stocky; she weighed 164 pounds (74 Kg.). The face and extremities presented a moderate grade of hypertrichosis.

The blood pressure was 120 systolic and 75 diastolic.

Roentgenograms of the sella turcica revealed no abnormalities.

Neurologic examination did not disclose any definite signs pointing to disturbances of the pituitary or adrenal glands. Nevertheless, the group of symptoms which the patient exhibited, namely, hypertrichosis, rapidly advancing obesity,

Fig. 2 (authors' case).—Eruption involving the intermammary and epigastric region.

irregular menstruation and possible hyperthyroidism, certainly aroused the suspicion of polyglandular imbalance, even to the casual observer.

Routine examinations of the blood, including a Wassermann test, urinalysis and examination of scrapings for fungi gave negative results. The basal metabolic rate was +22 per cent.

Skin: The eruption implicated almost all the surfaces of the body, in varying degree. It was most pronounced and of greatest intensity on the upper portion of the chest, on the neck and shoulders, in and around the axillae, on the lateral

surfaces of the breasts, on the intermammary and epigastric regions, on the antecubital and inguinal areas and on the middle portion of the lumbar region. The scalp, palms and soles were unaffected, and the buttocks and upper and lower extremities exhibited only isolated groups of lesions. On the chin and periorbicular area there was a mottled brown pigmentation resembling chloasma.

Fig. 3 (author's case).—Atrophic, glistening striated lesions and groups of flat papules involving the axillary region and the lateral aspect of the mammary region.

The skin of the neck was darkly pigmented; the natural folds were exaggerated, and the cutaneous markings were prominent. The surface exhibited a finely lamellated scaling which could be removed in the form of mealy lamellae rather than scales when scratched with the finger-nail. There were no definitely outlined papules on the neck.

The upper portion of the chest, the superior aspects of the shoulders and the upper portion of the back exhibited a widespread darkly pigmented papulosquamous eruption, the papules retaining their individual outlines in some areas but merging into confluent islands in others. The most conspicuous portion of the eruption was on the intermammary and on the epigastric region. The impression gained was that the eruption had spread peripherally from this region (which was indeed its starting point) to extend in the midsternal area upward toward the chest and shoulders and downward toward the umbilicus. The eruption on the intermammary and epigastric regions formed a roughly rhomboid outline, the long axis of

Fig. 4 (authors' case).—Papules covered with mealy scales, exaggerated cutaneous markings and dilated follicles involving the lumbar region.

which was longitudinally disposed. From these primarily affected areas the eruption appeared to have extended over the shoulders, involving the middle portion of the back from the neck to the intergluteal fold, and anteriorly downward toward the groins and internal aspects of the thighs.

The antero-external surfaces of the breasts and the skin surrounding the axillae exhibited grouped and longitudinally disposed striated formations. Clinically these were definitely atrophic and somewhat glistening on the lateral surfaces of the breasts and in the axillae; on the anterior surface of the breasts, which were pendulous, the papules stood out as distinct elevated lesions, some being isolated, others tending toward confluence. (The atrophic, somewhat depressed striated

lesions were like those observed on the breasts of patients with Cushing's pituitary basophilism.)

On the intermammary and epigastric areas the eruption closely simulated pityriasis versicolor. It consisted of confluent brownish yellow scarcely elevated papules merging into a triangular fused plaque in the central portion and gradually forming a network of diminishing intensity toward the lateral portions of the thorax and toward the umbilicus. Scratching the surface produced a mealy scaling which crumbled under the finger-nail.

The antecubital areas exhibited the most pronounced and well defined papular elements. Here there were groups of between 75 and 100 papules in each fossa, the lesions being more numerous on the right side. Some of these were confluent; others were isolated. Some were dark red, flat and from 1 to 2 mm. in diameter, their surfaces being thickened and rough but not scaly. Others in the same area were dark brown and moderately elevated and had a warty appearance. The larger lesions varied from 3 to 4 mm. in diameter, were dirty brown, and showed a thickened surface; some were covered with a sort of granular deposit. None of the papules was indurated. The edges of some were sharply defined; those of others merged imperceptibly with the surrounding skin. Scratching these papules with the finger-nail changed a dirty brown to a rather bright red papule but produced neither bleeding nor serous exudation.

In and around the axillae the skin was somewhat thickened and rugose, being studded with many elongated lesions with glistening surfaces which appeared to have undergone atrophy.

Over the entire length of the spine the skin was studded with isolated, grouped and confluent flat yellowish brown papules, the surfaces of which had a lamellated scaly appearance and a somewhat oily feel. The cutaneous markings were greatly exaggerated, the change being most pronounced in the lumbar area.

The visible mucosae and the nails were unaffected. Subjective symptoms were absent.[3]

*Histologic Examination* (fig. 5).—A section from a papule from the middle portion of the epigastric region was stained with hematoxylin and eosin. Microscopic examination revealed a pronounced hyperkeratosis, manifested by a densely laminated horny layer below which the epidermis was thinned; the prickle cell layer was reduced in width; the surface configuration was irregular and wavy, some of the papillary bodies with overlying epidermis extending upward in places, surmounting the mean level of the epidermal outline. The granular layer consisted of a single row of cells. The prickle cells were small and rounded; their nuclei were deeply stained and round and contained distinct nucleoli. The prickles were not visible. Some mitotic figures were present. In some zones the nuclei appeared to be more or less solid, all being laterally situated toward the same

3. A remarkable complication, in the nature of a coexisting dermatosis, and one seemingly independent of the papillomatosis consisted of the following clinical manifestations: On the middle region of the anterior aspect of both arms (more marked on the right) were well defined groups of round glistening ivory yellow papules the size of the head of a small pin (fig. 1) arranged in longitudinal linear configuration. They were absent on other parts of the body. The patient noticed that they were quite different from her other eruptions, but she did not know how long they had been present. Clinically these papules were indistinguishable from lichen nitidus. Histologically, however, their structure was definitely tuberculoid.

pole of the cell. The protoplasm was lacking, while the cell outline was distinct. The basal cell margin was unaltered.

The papillary bodies were elongated. The vessels of the upper portion of the cutis were only slightly dilated, and about them there was a mild cellular infiltrate composed of small round cells. The vessel walls were unaltered. The single hair follicle in the section was shrunken, its walls were thinned and its lining cells showed the same changes as those noted in the epidermis. The sebaceous gland

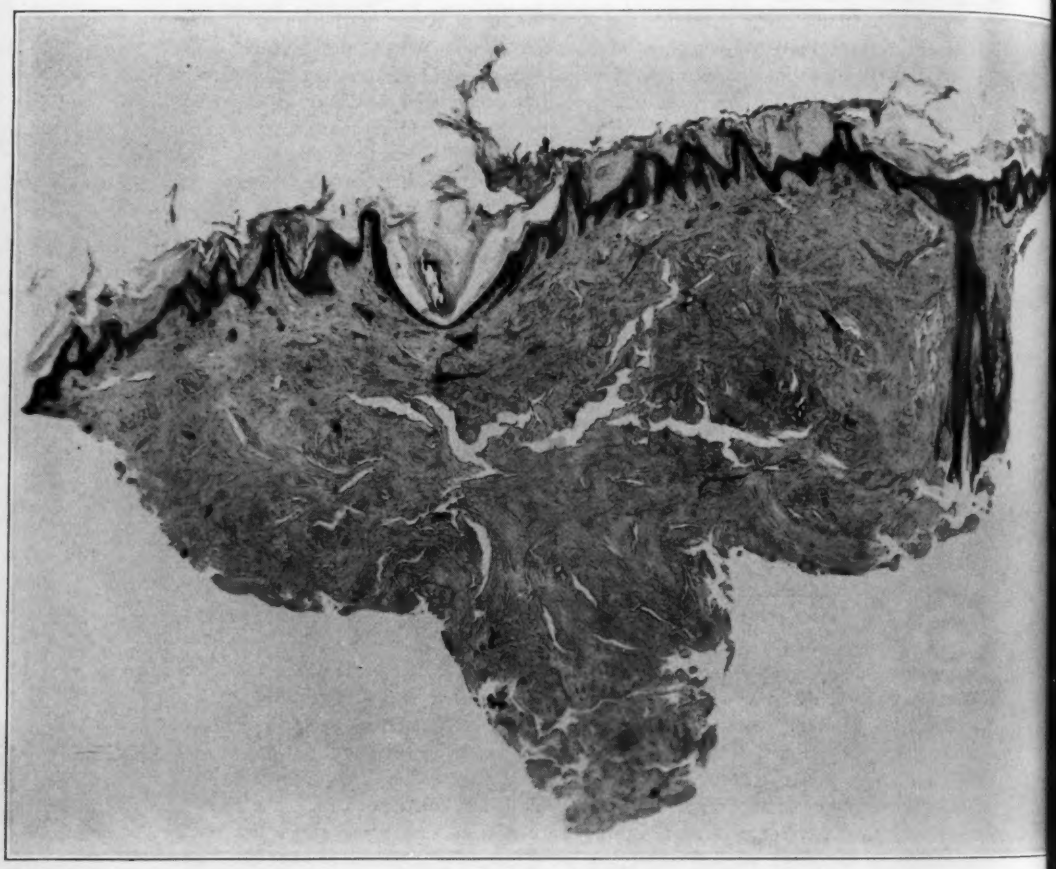

Fig. 5 (authors' case).—Section from a flat papule removed from the epigastric region.

was atrophied and consisted of only a few small cells. Sweat glands were absent in the section. Other areas of the cutis exhibited no deviations from the normal.

Elastic tissue stain revealed a normal elastica in the upper portion of the cutis; in the lower portion the elastic tissue was frayed and clumped.[4]

4. Variations in the histologic structure were summarized by Gougerot and Carteaud in the description of the three groups of papillomatosis they studied. The chief features were as follows: (1) there was lamellated hyperkeratosis without abscess formation; (2) a moderate grade of papillomatosis was present;

*(Footnote continued on next page)*

*Course and Treatment.*—The patient was directed to anoint the affected areas with an ointment composed of 6 per cent salicylic acid and 4 per cent ammoniated mercury in a base of hydrous wool fat. The areas which were diligently treated readily cleared up. However, within a few days after the cessation of treatment with this ointment the isolated and fused papules reappeared, although in the intervening period the skin appeared fairly normal to the naked eye. The patient is still receiving active treatment at the time of writing. Should the dermatosis prove to be recalcitrant to the conventional topical remedies, fractional doses of roentgen radiation will be administered.

Fig. 6 (fig. 1, Gougerot and Carteaud [1]).—Confluent and reticulated papillomatosis.

(3) the epidermis was sinuous and the rete somewhat atrophic; (4) the basal cell layer did not present uniform palisade configuration; the prickle cells had lost their intercellular filaments; the stratum granulosum was in part absent; in other parts it was composed of a single row of flattened cells, poor in keratohyalin; (5) there were moderate perivascular infiltrates in the cutis; (6) the hair follicles and sebaceous glands were unaltered (they were atrophic in our case); (7) the sweat glands were absent; (8) the elastica was unchanged in the region of the papillary bodies and frayed in the deeper layers of the cutis, forming short, fine stumps, which, however, retained their tinctorial qualities.

Fig. 7 (fig. 2, Gougerot and Carteaud [1]).—Eruption involving the intermammary and epigastric region.

Fig. 8 (fig. 7, Gougerot and Carteaud [1]).—Section showing lamellar hyperkeratosis, papillomatosis and atrophy of the stratum Malpighi.

## COMMENT

As stated, both the clinical and the histologic changes in our patient were almost a replica of those in the typical case of group II of Gougerot and Carteaud (figs. 6, 7 and 8).

These authors, in their comprehensive article, include a thorough discussion of differential diagnosis from other dermatoses with which their groups of papillomatoses might be confused; among these, they stress the following conditions: epidermodysplasia verruciformis, verrucae planae juveniles, Darier's disease and acanthosis nigricans. These differentiations, as well as the differentiations of the dermatoses of group II from those of groups I and III, are given in the text and also in all-inclusive tables.

## CONCLUSIONS

An example of the papillomatosis classified by Gougerot and Carteaud as group II of "new forms of papillomatoses" is described, clinical and histologic features being given.

Attention is directed toward the fact that in our patient the eruption and the microscopic structure of the lesions were astonishingly similar to those in the typical case described by these authors under their group II, namely, *papillomatose confluente et réticulée.*

The American literature contains no reference to this group of dermatoses; hence the publication of an isolated example appears to be warranted in the expectation that cases of a similar condition will soon be encountered.

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# DIAGNOSTIC VALUE OF THE INTRADERMAL CHANCROIDAL TEST

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The title of this paper is somewhat presumptuous in that it implies that the intradermal chancroidal test is diagnostic. We wish to modify this premise, for if the evidence we are to present is to carry any weight, we must not attempt to prove all that the title infers.

1. This paper deals with two different intradermal tests so far as in one a pus antigen is used and in the second a bacillary antigen is employed.

2. This paper, in reality, is merely an evaluation of these two tests in the diagnosis of infection by the bacillus of Ducrey.

3. This paper attempts to prove the superiority of the test with bacillary antigen as advocated by us [1] over the test with pus antigen described by Cole and Levin.[2]

In the routine work of a special clinic organized at the University Hospital for the study of the so-called newer venereal diseases, namely, granuloma inguinale and lymphogranuloma venereum, certain observations proved confusing. In the preparation of Frei antigen from pus from buboes of patients who exhibited a positive reaction to Frei tests an antigen was occasionally prepared which failed to elicit a positive reaction in patients known to have lymphogranuloma venereum. This antigen, however, provoked a positive response in certain patients with typical chancroidal infection. The full significance of this observation was appreciated only when Cole and Levin's article appeared describing the intradermal reaction for chancroids with pus from chancroidal buboes. Our interest in this subject naturally deepened, for we foresaw the

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Read before the Dugas Journal Club of the University of Georgia School of Medicine, Dec. 21, 1936.

From the Department of Pathology and the Department of Bacteriology and Public Health, University of Georgia School of Medicine.

1. (*a*) Greenblatt, R. B., and Sanderson, E. S.: Chancroidal Vaccine: A Method of Preparation; Its Diagnostic and Therapeutic Value, Am. J. Clin. Path. **7**:193 (March) 1937; (*b*) Sanderson, E. S., and Greenblatt, R. B.: The Cultivation of Hemophilus Ducreyi and Preparation of an Antigen for Intracutaneous Diagnosis of Chancroidal Infection, South. M. J. **30**:147 (Feb.) 1937.

2. Cole, H. H., and Levin, E. A.: The Intradermal Reaction for Chancroids with Chancroidal Bubo Pus, J. A. M. A. **105**:2040 (Dec. 21) 1935.

possible errors in determining the etiology of any one bubo unless both a Frei and an intradermal chancroidal test were made.

Furthermore, we soon encountered cases of typical buboes in which a positive reaction to neither a Frei nor an intradermal chancroidal test could be obtained. The source of error was determined in cultures, clotted rabbit's blood medium being used according to the method of Teague and Deibert.[3] This failure of the pus from chancroidal buboes to evoke a positive cutaneous reaction in some cases of disease proved by cultural methods to be due to the Ducrey bacillus is subject to interpretation. The antigenic properties contained in the pus from some buboes is insufficient to excite an allergic reaction in certain patients with chancroidal bubo. The need for a test giving more uniform results became evident.

### PREPARATION OF DUCREY ANTIGEN FOR INTRADERMAL TESTS

Because of these observations we set out to find the most suitable method for the cultivation of the Ducrey bacillus which would lend itself with facility to the preparation of a saline suspension of bacilli for use as an antigen in the intradermal test. A method which could be generally acceptable because of its relative simplicity[4] and accuracy has been described by us in the *American Journal of Clinical Pathology*[1a] and in the *Southern Medical Journal*.[1b]

We have met with little success in growing the organism on the surface of any medium in amounts sufficient to be utilized for suspensions. The following method has therefore been used:

To tubes of beef infusion agar in slants is added 1 cc. of defibrinated human blood. The blood is inoculated with 0.1 cc. from an actively growing culture and placed under partial oxygen tension. To obtain this environment, the cotton plug is cut off short and pushed slightly into the tube; the upper portion of the tube is heated, but not too much, in a Bunsen flame, and the tube is sealed by inserting a tightly fitting rubber stopper. The culture is incubated for from two to three days at 37 C. During this period good growth takes place in the fluid blood, and a lesser growth appears on the surface of the slant. After the incubation, the blood as well as the surface growth, if any, is removed with a sterile pipet and added to approximately 25 cc. of sterile distilled water in a sterile centrifuge tube of sufficient volume, and the contents are sedimented by high speed centrifugation. The supernatant fluid is removed aseptically and discarded, and the process is

3. Teague, O., and Deibert, O.: The Value of the Cultural Method in the Diagnosis of Chancroid, J. Urol. **4**:543 (Dec.) 1920.

4. A vaccine prepared by G. A. Hunt (Cultivation of Ducrey Bacillus for Preparation of Vaccine, Proc. Soc. Exper. Biol. & Med. **33**:293 [Nov.] 1935) has been tried out by us and found to match our bacillary antigen, but we have found it difficult to prepare this vaccine. In Europe and in Canada Dmelcos vaccine is used; this is relatively expensive and is not readily available in the United States. Moreover, our antigen and the Dmelcos vaccine gave identical cutaneous reactions in a controlled series of cases.

repeated. Two such treatments suffice to remove most of the hemoglobin. The sediment of bacilli and red cell débris are suspended in sterile physiologic solution of sodium chloride, 10 cc. per slant being placed in sterile vials, and heated for thirty minutes at 60 C. A 1:10,000 solution of merthiolate is used as a

TABLE 1.—*Analysis of Intradermal Chancroidal Tests*

| | | |
|---|---|---|
| Number of tests performed | | 721 |
| Total number of patients tested | | 191 |
| Number of patients tested with both bacillary antigen and pus antigen | 104 | |
| Number of patients tested with either bacillary antigen or pus antigen | 87 | |
| | | 191 |
| Number of patients showing a positive reaction to the chancroidal test | 80 | |
| Number of patients showing a negative reaction to the chancroidal test | 111 | |
| | | 191 |

TABLE 2.—*Evaluation of the Reaction to Bacillary Antigen and to Pus Antigen in the Same Patient*

| | | |
|---|---|---|
| Number of patients tested with both bacillary antigen and pus antigen | | 104 |
| Of 53 patients showing a positive reaction to the bacillary antigen | | |
| The response to pus antigen matched in | 34 | |
| The response to pus antigen did not match in | 19 | |
| | 53 | |
| Of 51 patients showing a negative reaction to bacillary antigen | | |
| The response to pus antigen matched in | 51 | |
| | | 104 |

TABLE 3.—*Comparison Between Results of the Chancroidal Test and Those of the Frei Test*

| | | |
|---|---|---|
| Of 80 patients showing a positive reaction to the chancroidal test | | |
| A positive reaction to the Frei test was elicited in | 24 | |
| A negative reaction to the Frei test was elicited in | 54 | |
| The Frei test was not performed in | 2 | |
| | | 80 |
| Of 111 patients showing a negative reaction to the chancroidal test | | |
| A positive reaction to the Frei test was elicited in | 69 | |
| A negative reaction to the Frei test was elicited in | 29 | |
| The Frei test was not performed in | 13 | |
| | | 111 |
| | | 191 |

preservative. One-tenth cubic centimeter is employed for intracutaneous tests, and the reactions are observed in forty-eight hours.

## RESULTS OF TESTS

A total of 721 intradermal chancroidal tests were performed on 191 patients. An analysis of these tests is given in table 1. It will be noted that 104 patients underwent tests with both the bacillary antigen and the antigen from bubo pus; this made it possible to draw conclusions as to the relative value of these two tests. In an evaluation

of this group (table 2) the discrepancies between the results of the two tests are readily discernible. The advantages of the test with bacillary antigen over the test with bubo pus antigen are made more evident when two additional facts are considered.

(*a*) In 11 cases of bubo from which Ducrey's bacillus was actually cultured a positive reaction to bacillary antigen was elicited, whereas in only 8 of these cases was a positive response to pus antigen obtained.

(*b*) Whenever the reaction to pus antigen was positive a similar response to bacillary antigen could be expected. The corollary to this, however, does not hold. For, as table 2 shows, of 53 patients giving

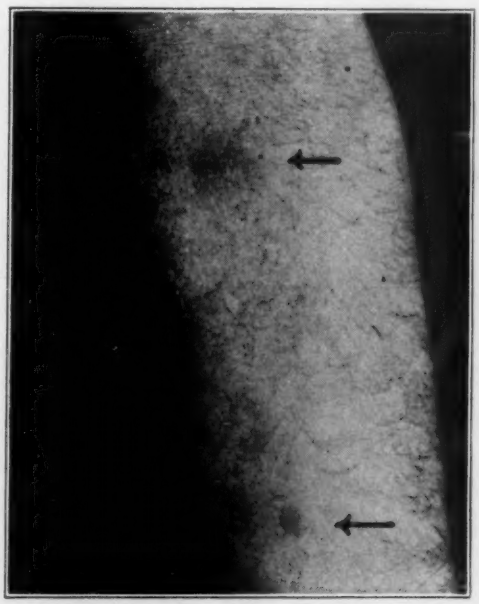

Fig. 1 (case 3).—Photograph showing the difference in the intensity of the response forty-eight hours after the intradermal injection of 0.1 cc. of bacillary antigen (*A*) and 0.1 cc. of pus antigen (*B*).

a positive reaction to bacillary antigen, 19 did not exhibit a corresponding reaction to pus antigen. In figure 1 the difference in the intensity of the reaction to bacillary antigen and the pus antigen is strikingly demonstrated.

The usefulness of the intradermal chancroidal test is evident from an analysis of table 3. The chancroidal test should accompany the Frei test as a routine. The information obtained by the routine use of both the chancroidal test and the Frei test is of much greater value in the diagnosis of any bubo than is that furnished by one or the other test performed alone. The very fact that in this series 24 patients responded

positively to both the chancroidal and the Frei test points out the need for caution in interpretation if but one test is employed. The importance of a negative reaction is amply borne out when the differential diagnosis between the bubo of lymphogranuloma venereum and that of chancroidal infection is considered. Of 80 patients exhibiting a positive reaction to the chancroidal test, 54 had a negative reaction to the Frei test, whereas of 106 patients who had a negative reaction to the chancroidal test, 69 had a positive reaction to the Frei test. This excluded the possibility of chancroidal infection or lymphogranuloma venereum, respectively, in the differential diagnosis.

Fig. 2 (case 1).—Chancroidal bubo undergoing breakdown and ulceration.

Although it is not in the scope of this paper to enter into the differential diagnosis of lesions of the inguinal region, a few photographs are presented. The cases are summarized to emphasize certain salient features.

## REPORT OF CASES

CASE 1 (fig. 2).—A man aged 42 came to the clinic of the University Hospital presenting a tender fluctuating bubo of two weeks' duration. Three weeks previously multiple small ulcers had been present at the coronal sulcus. This patient reacted negatively to Frei antigen. The Wassermann and Kahn tests were negative. The bubo was aspirated. A positive culture of Ducrey's bacillus was obtained. A bacillary antigen was prepared from this culture, and from pus from the bubo an antigen was prepared. To the test with bacillary antigen the patient always reacted positively. He reacted positively to some strains and negatively to

other strains of antigen prepared from the pus of buboes. The pus antigen prepared from his own bubo pus frequently failed to elicit a positive response in other patients known to have chancroidal infection. The diagnosis was chancroidal bubo.

CASE 2. (fig. 3).—A Negress aged 26 on examination at the clinic was found to have a peculiar raised granulomatous ulceration in the right inguinal region. This lesion was cleancut and raised at the margins and slightly necrotic in its central portion. The ulceration was not preceded by any vulvar lesion. Since the Frei antigen and chancroidal bacillary antigen and pus antigen elicited negative reactions, these results ruling out both lymphogranuloma venereum and chancroidal infection, it was decided to look for Donovan bodies. Smears from the lesion were loaded with Donovan bodies. The diagnosis was pseudobubo of granuloma inguinale.

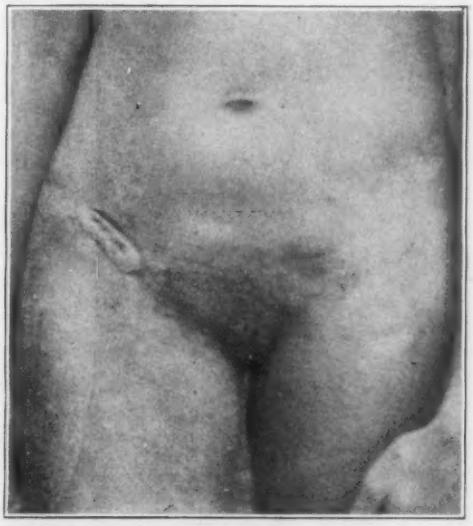

Fig. 3 (case 2).—Pseudobubo of granuloma inguinale. This lesion must be differentiated from the lesion in case 1 and from that in case 4.

CASE 3 (fig. 4).—A man aged 32 came to the clinic presenting a lesion of the inguinal region which refused to respond to treatment. Several lesions were also present on the prepuce. The lesions in the groin were spreading by extension and auto-inoculation. The Wassermann and Kahn tests were positive. The Frei test was negative. Tests with chancroidal bacillary antigen were repeatedly positive. Tests with chancroidal pus antigen were negative or occasionally weakly positive (fig. 1). Smears failed to show Donovan bodies or Spirochaeta pallida. A superimposed fusospirillosis, however, was also noted.[5] The diagnosis was chancroidal infection.

CASE 4.—A Negress aged 30 came to the clinic exhibiting a series of ulcerations in the left inguinal region. She had a small ulcer within the labium minus pudendi, which was covered with a yellow gelatinous exudate. Wassermann and

5. Greenblatt, R. B., and Wright, J.: The Significance of Fusospirillosis in Genital Lesions, Am. J. Syph., Gonor. & Ven. Dis. **20**:654 (Nov.) 1936.

Frei tests were negative. Smears and microscopic examination of sections showed no Donovan bodies. Positive reactions to chancroidal bacillary and to pus antigen were obtained. The diagnosis was chancroidal infection.

## CONCLUSIONS

In conclusion, several points must again be stressed. An accurate diagnosis in almost every case of genital lesion is not only possible but necessary. No one is justified in diagnosing a genital lesion without the aid of the laboratory.

Fig. 4 (case 3).—Chancroidal ulceration of the groin spreading by extension and auto-inoculation simulating various manifestations of the other venereal diseases.

In many instances the venereal diseases resemble one another so closely as to confuse the clinical picture.[6] An additional factor in this confusion is the similarity in names, such as chancre and chancroid, lymphogranuloma inguinale (lymphogranuloma venereum) and granuloma inguinale. It should be remembered that just as chancre and chancroid may occur simultaneously, making a clear distinction difficult, so too may all the venereal diseases occur in any combination or permutation. The Frei test remains positive for life once lymphogranuloma venereum has been contracted. The reaction to the intradermal chan-

6. Greenblatt, R. B.; Sydenstricker, V. P., and Pund, E. R.: The Fourth and Fifth Venereal Diseases, J. M. A. Georgia **26**:16 (Jan.) 1937.

croidal test remains positive for life, although occasionally temporary periods of anergy are reached after several injections.

The fact that the reactions to these tests remain positive for life should be borne in mind when the intradermal reactions are interpreted. A positive response is only presumptive evidence and does not necessarily mean that the lesion under consideration is lymphogranuloma venereum or chancroidal infection. For this reason we have, earlier in this paper, modified the premise inferred by the title. The reaction is of value when it is negative, for it rules out chancroidal disease, but this is true only when the bacillary antigen is employed. We have shown that the antigen prepared from the pus from buboes frequently produces a negative reaction even in cases in which the diagnosis has been proved culturally. Reactions to the bacillary antigen are far more accurate.

Finally, a positive response to a chancroidal test, whether pus antigen or bacillary antigen is used, commits one to the diagnosis of chancroidal infection only when the Frei test, the Wassermann test and histopathologic examination for malignant disease and for granuloma inguinale [7] give negative results.

## SUMMARY

A total of 721 intradermal chancroidal tests were performed on 191 patients, and conclusions are drawn as to the diagnostic value of the test.

The superiority of the chancroidal test with bacillary antigen as advocated by us over the test with antigen prepared from the pus from buboes as described by Cole and Levin is evaluated.

A warning note is sounded to investigators who report cases of lymphogranuloma venereum on the basis of a positive Frei test without performing a concurrent chancroidal test. Twenty-four patients in a group of 80 patients exhibiting a positive reaction to the chancroidal test also had a positive reaction to the Frei test; this emphasized the need for caution in the interpretation of the results of these tests.

A positive chancroidal test is only presumptive evidence and does not necessarily mean that the lesion under consideration is chancroidal. A similar conclusion should be borne in mind in the interpretation of a positive Wassermann as well as of a positive Frei test in every case of genital lesion unless other confirmatory laboratory evidences are present.

Finally, a negative intradermal test with bacillary antigen is diagnostic so far as it rules out infection by the bacillus of Ducrey. A positive intradermal chancroidal test commits one to the diagnosis of chancroidal infection only when the Frei test, the Wassermann test and microscopic examinations for malignant disease and granuloma inguinale give negative results.

7. Pund, E. R., and Greenblatt, R. B.: Specific Histology of Granuloma Inguinale, Arch. Path. **23**:224 (Feb.) 1937.

# RELATIONSHIP OF THE URTICARIAL TO THE INFLAMMATORY REACTION TO TRICHOPHYTIN

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In recent years an interesting insight into the relationship of immediate to delayed reactions has been given by Tezner,[1] Simon and Rackemann,[2] Rudolph and Cohen[3] and others. By experiments on immunization with albumin, pollen and ascaris antigen Tezner has demonstrated that in the course of the immunization the two forms of reaction occur in a definite cycle in a normal person. The delayed reaction appears first and is followed a week later by an immediate reaction. During the further course of the immunization the delayed reaction disappears and then the immediate reaction. On the other hand, in immunization (desensitization) of an allergically hypersensitive (atopic) person there is no delayed reaction, and only a slight diminution of the primary immediate reaction is observed. However, a delayed reaction can occasionally be produced by immunization of a person whose hypersensitivity is less marked. Consequently, Tezner concluded that there is a qualitative difference between the reactions to the same allergen of an allergically predisposed person and a normal person. This is confirmed by Touart's[4] experience with bacterial allergens and by the observations of Cooke and Spain,[5] Otto and Adelsberger[6] and Rudolph and Cohen concerning primary and acquired hypersensitivity toward serum. Rackemann maintained that the differ-

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From the Dermatologic Clinic of the Finsen Institute, Svend Lomholt, M.D., Director.

1. Tezner, O.: Arch. f. Dermat. u. Syph. **170**:293, 1934; Jahrb. f. Kinderh. **142**:69 and 220, 1934; Klin. Wchnschr. **14**:539 (April 13) 1935; Jahrb. f. Kinderh. **145**:86, 1935.

2. Simon, F. A., and Rackemann, F. M.: J. Allergy **5**:439, 1934.

3. Rudolph, J. A., and Cohen, M. B.: Types of Human Hypersensitiveness: Their Relationship to Liability to Serum Reactions, J. A. M. A. **102**:900 (March 24) 1934.

4. Touart, M. D.: J. Allergy **5**:627, 1934.

5. Cooke, R. A., and Spain, W. C.: J. Immunol. **17**:295, 1929.

6. Otto, R., and Adelsberger, L.: Ztschr. f. Hyg. u. Infektionskr. **113**:16 1931.

ence between atopic and sensitized normal persons is purely quantitative. Nevertheless, the results of experiments by György, Moro and Witebsky [7] strongly indicate that the two forms of reaction are due to two different antibodies to the same antigen, which bind complement in two distinct zones of dilution. There is no evidence as yet to show whether the two reactions are due to separate components of the antigen, but Dienes,[8] Bosch, György and Witebsky,[9] and Caulfeild, Brown and Waters [10] have pointed out that some of the allergen solutions in general use consist of several components with different effects. Owing to the rare occurrence in clinical practice of immediate and delayed reactions evoked by the same diagnostic or therapeutic substance, the study of these matters has been made possible chiefly by sensitization experiments. Protein extracts seldom produce delayed reactions; tuberculin produces immediate reactions only in rare cases. Trichophytin, however, occasionally produces an immediate reaction besides the diagnostic delayed reaction. This immediate reaction is of particular interest owing to its being fully elucidated in spite of the limited number of cases described. Moreover, because of the fact that the immediate reaction is easily transmitted by means of the Prausnitz-Küstner experiment to the skin of normal persons responding to trichophytin, the occurrence of the immediate and of the delayed reaction in the same tissue is assured.

The first case of an immediate reaction to trichophytin was reported by Sulzberger and Kerr,[11] who gave a full account of its specificity and transmissibility. Since then cases have been reported by Wise and Sulzberger,[12] Ramirez,[13] Goldsmith,[14] Quero,[15] Bernton and Thom,[16] Tomlinsson [17] and Pennington,[18] confirming the transmissi-

7. György, P.; Moro, E., and Witebsky, E.: Klin. Wchnschr. **9**:1012 (May 31) 1930; **11**:1172 (July 9) 1932.

8. Dienes, L.: J. Immunol. **20**:333, 1931.

9. Bosch, E.; György, P., and Witebsky, E.: Ztschr. f. Kinderh. **53**:394, 1932.

10. Caulfeild, A. H. W.; Brown, M. H., and Waters, E. T.: J. Allergy **7**:1, 1935.

11. Sulzberger, M. B., and Kerr, P. S.: J. Allergy **2**:11, 1930.

12. Wise, F., and Sulzberger, M. B.: Urticaria and Hay-Fever Due to Trichophytin (Epidermophyton Interdigitale), J. A. M. A. **95**:1504 (Nov. 15) 1930.

13. Ramirez, M. A.: M. J. & Rec. **132**:382 (Oct. 15) 1930.

14. Goldsmith, W. N.: Brit. J. Dermat. **43**:121, 1931.

15. Quero, R.: Bol. Soc. cubana de dermat. **2**:91, 1931.

16. Bernton, H. S., and Thom, C.: J. Allergy **4**:114, 1933.

17. Tomlinsson, W. J.: J. Allergy **6**:573, 1935.

18. Pennington, E. S.: J. Allergy **7**:54, 1935.

bility, specificity and group specificity of the reaction (Tomlinsson). Several of the patients displayed general allergic symptoms after the injection (Ramirez, Wise and Sulzberger, Quero). Sulzberger and Wise [19] pointed out the importance of sensitivity to trichophytin as an etiologic factor in urticaria, hay fever and allergic eczema (Ramirez referred specifically to asthma), and Sulzberger consequently coordinated the immediate reaction with the delayed reaction and the epidermal reaction (Sulzberger and Lewis [20]). Finally, Bernton and Thom gave prominence to the frequent occurrence of the immediate reaction in allergically predisposed patients. The fact that in most of the cases reported there were no allergic symptoms but the reactions were discovered by chance may explain why so few cases have been described. A patient is seldom inspected immediately after the injection of trichophytin; he is inspected from twenty-four to forty-eight hours later, when the delayed reaction is expected to have set in. Thus in many cases the immediate reaction is overlooked and is either discovered by the patient or manifested by general symptoms or by the nonappearance of the delayed reaction frequently attendant on the immediate reaction, which is inconsistent with the record (deep mycosis of long duration) and gives rise to a revision of the case. At all events, Bernton and Thom's 12 cases occurring among 400 patients indicate that the incidence is not infrequent.

Within three months I have had occasion to observe 8 cases of urticarial reaction to trichophytin and have thus been able to carry out a number of experiments with the same dilutions of antigen and to control their strength by means of control tests on each patient.

## REPORT OF CASES

As the cases have many points of resemblance, I shall give a short summary of them.

CASE 1.—C. B., a man aged 38, a brewery hand, stated that there was no allergic predisposition in his family. His health had been good previously. He had never had a cutaneous disease, asthma or hay fever but had suffered from urticaria of unknown origin for several months. The attacks had occurred for short periods, and the localization had varied greatly. For two years he had had mycotic eczema localized to interstices of the toes; this was resistant to every treatment.

19. Sulzberger, M. B., and Wise, F.: Ringworm and Trichophytin: Newer Developments, Including Practical and Theoretical Considerations, J. A. M. A. **99**:1759 (Nov. 19) 1932.

20. Sulzberger, M. B., and Lewis, G. M.: Trichophytin Hypersensitiveness Demonstrated by Contact Tests: Preliminary Report, Arch. Dermat. & Syph. **22**:410 (Sept.) 1930.

The diagnosis was epidermophytosis pedis.

The Wassermann reaction was negative; the Mantoux reaction was positive with a 1:100,000 dilution; patch tests with substances likely to cause eczema and with thirty-eight protein extracts were negative. There was no dermographism.

The results of the other tests were as follows:

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (+ +) (wheal 20 by 25 mm.; reflex erythema 54 by 80 mm.; pseudopods, 3) delayed reaction negative |
| Scarification with trichophytin (1:1 dilution) | 16 mm.; reflex erythema; pseudopods |
| Patch test with trichophytin (1:1 dilution) | Negative |
| Test with epidermophytin (0.05 cc. intracutaneously) | Immediate reaction, positive (wheal, 18 by 18 mm.; reflex erythema, 45 mm.; pseudopods, +) delayed reaction, negative |
| Trichophytin titer | $10^{-4}$ (wheal, 12 by 14 mm.; reflex erythema positive; 1 pseudopod) |
| Prausnitz-Küstner reaction | 19 experiments, positive; 25 experiments, negative (percentage of "takes," 43) |
| Histamine (1:1,000 dilution) | Wheal, 20 by 36 mm.; reflex erythema, 70 by 100 mm. |
| Desensitization (12 injections of 0.1 cc. of desensitizing substance) | Reaction unaltered (wheal, 17 by 30 mm.; reflex erythema, 70 by 85 mm.) |

CASE 2.—P. S. J., a man aged 45, a commercial traveler, stated that there was no allergic predisposition in his family. His health had been good previously. He had never had asthma, hay fever or urticaria. For fifteen years he had had eczema of the left sole; this had been continuously treated with application of silver nitrate and bathing with alcohol, but no improvement had resulted. Just before the patient presented himself at the clinic there had occurred an exacerbation associated with infection and acute lymphangitis; this had been treated with antiseptics and hot cataplasm.

Eczema localized to the interstices of the toes was found; fissures, maceration and peeling were noted; on the sole was a plaque of eczema, 4 by 6 cm., with lamellar marginal peeling. The clinical picture was typical of mycoses, but repeated examinations revealed no fungi (this may have been due to the antiseptic treatment). Complete healing resulted in three weeks of treatment with ethyl paraoxybenzoate.

The diagnosis was eczema of the left foot.

The Wassermann reaction was negative; patch tests with substances likely to cause eczema and with thirty-eight protein extracts were negative. There was no dermographism.

The results of the other tests are given in the following tabulation.

| | |
|---|---|
| Tests with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | After ten minutes, violent edema of the face and backs of the hands, general urticaria, asthma collapse (The attack was completely over in two hours.) |
| (0.1 cc. of 1:10,000, dilution intracutaneously) | Immediate reaction, positive (wheal, 14 by 18 mm.; reflex erythema, 30 by 40 mm.; 2 pseudopods) delayed reaction, negative |
| Scarification with trichophytin (1:1 dilution) following application of a tourniquet | 33 mm. (followed by edema of the arm) |
| Patch test with trichophytin | Negative |
| Trichophytin titer | $10^{-5}$ |
| Prausnitz-Küstner reaction | 23 experiments, positive; 6 experiments, negative (percentage of "takes" 79) |

Case 3.—I. B., a girl aged 19, a typist, had a sister who suffered from urticaria and facial edema after she ate lobster. The patient had formerly been healthy and had never displayed allergic symptoms. During the summer of 1934 mycotic eczema appeared on the left foot. Culture of material from the involved area showed Epidermophyton interdigitale. The condition disappeared in two months after treatment. Since then the patient had periodic urticarial eruptions on the trunk and extremities. In January 1936, after she had been on a walking tour, there appeared a bulla about the size of the palm of one's hand occupying the whole site of the previous eruption. Culture showed Epidermophyton interdigitale. As a result of antimycotic treatment the condition disappeared in three months.

The diagnosis was epidermophytosis of the left foot.

The Wassermann reaction was negative; a patch test for eczema was negative. There was no dermographism.

The results of other tests are given in the following tabulation.

| | |
|---|---|
| Protein tests (scarification) | Goose feathers, 6 mm.; Avena pollen, 10 mm.: Dactylis pollen, 5 mm.: maize, 9 mm. |
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (+++) (20 minute reaction: wheal, 26 by 34 mm.; reflex erythema 65 mm.; pseudopods, numerous) |

This reaction was hyperergic, the results being as follows:

35 minutes: wheal, 40 by 44 mm.; reflex erythema, 65 mm.; pseudopods, numerous

45 minutes: wheal, 50 by 50 mm. (not sharply defined)

52 minutes: wheal, 55 mm. (not sharply defined); reflex erythema, 90 mm. (diffuse)

2 hours: infiltration 90 mm.; diffuse edema
24 hours: deep infiltration 60 mm.; no reflex erythema; no edema
48 hours: all manifestations disappeared; delayed reaction, negative

| | |
|---|---|
| Scarification with trichophytin (1:1 dilution) | 15 mm. |
| Patch test with trichophytin (1:1 dilution) | negative |
| Trichophytin titer | $10^{-18}$ |
| Prausnitz-Küstner reaction | 20 experiments, positive; none negative |

Fig. 1.—Exanthematic trichophytid.

CASE 4.—K. O., a youth aged 16, a farm hand, showed no allergic predisposition. His previous health had been good. He tended live stock in a stable where a cow had ringworm. The patient had had an abscess on the neck for three weeks, and two days before he was seen a sudden eruption of itching exanthem had developed on the back and chest. A kerion with numerous perforations was observed on the patient's chin, and Trichophyton gypseum-asteroides was observed. On the back and on the chest there was an exanthem consisting of confluent blotches with a slightly elevated red margin and a paler center in which fine peeling subsequently appeared (fig. 1).

The diagnosis was trichophytosis; kerion; exanthematic trichophytid.

The Wassermann test, patch tests with substances likely to cause eczema and tests with protein extracts gave negative results. There was no dermographism.

The results of other tests were as follows:

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (wheal, 15 by 22 mm.; reflex erythema, 45 by 45 mm.)<br>delayed reaction (?) (after 72 hours an exanthematic plaque developed; it disappeared in 14 days, leaving fine scales [fig. 2]) |
| Scarification with trichophytin (1:1 dilution | Negative |
| Patch test with trichophytin (1:1 dilution) | Negative |
| Trichophytin titer | $10^{-2}$ |
| Prausnitz-Küstner reaction | 14 experiments, negative (percentage of "takes," 0) |

Case 5.—R. L., a man aged 22, a butcher, stated that a sister had urticaria caused by oranges. He had always been well and had never noted symptoms of allergy. A double circle ringworm of one month's duration was present on the right forearm, and T. gypseum-asteroides was observed.

The diagnosis was trichophytosis.

The Wassermann test and patch tests with substances likely to cause eczema were negative. Tests with protein extract showed a 4 mm. reaction for shrimps. There was no dermographism.

The results of other tests were as follows:

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (++) (wheal, 22 by 18 mm.; reflex erythema, 40 by 60 mm.; pseudopods, 1)<br>delayed reaction, negative |
| Scarification with trichophytin (1:1 dilution) | Negative |
| Patch test with trichophytin (1:1 dilution) | Negative |
| Trichophytin titer | $10^{-3}$ (wheal, 12 by 14 mm.; reflex erythema, 32 mm.) |
| Prausnitz-Küstner reaction | 1 experiment, positive; 7 experiments negative,<br>(percentage of "takes," 12) |

Case 6.—A. S., a woman aged 34, a domestic servant, stated that her mother and two siblings had allergic eczema and two other siblings had asthma. A brother also suffered from the same trouble as the patient. She had had adenitis colli and chilblains in childhood and suffered from eczema which had been localized to the ears from her fifteenth year and had involved the neck and arms during the past two years. Lately she had been affected with vasomotor rhinitis, which developed after she had been in a cow shed. During a summer a few years before the patient had eczema with fissures in the

interstices of the toes which disappeared in a few weeks after treatment with ointment. Later she had vesicular eruptions along the sides of the fingers every summer for several years.

The diagnosis was generalized allergic eczema.

The Wassermann test and patch tests with substances likely to cause eczema gave negative results. Tests with extracts gave results as follows: a test with lactalbumin, a 6 mm. reaction; a test with lactoglobulin, a 5 mm. reaction; a test with rice, a 5 mm. reaction.

The results of other tests are given in the tabulation.

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (wheal, 13 by 19 mm.; reflex erythema, 50 by 60 mm.)<br>delayed reaction, negative |
| Scarification and patch test with trichophytin | Negative |
| Trichophytin titer | $10^{-2}$ (wheal, 10 by 13 mm.; reflex erythema, 50 by 60 mm.) |
| Prausnitz-Küstner reaction | 10 experiments, negative |

CASE 7.—E. C. was a girl aged 10 years. Her paternal grandmother suffered from asthma, and two paternal uncles and a cousin had the same cutaneous disease as the patient. She had had eczema from the age of 2 months; the condition had originally been localized to the face and scalp; later it had involved the area around the mouth and the flexures of the elbows and knees, and periodical eruptions had appeared on other parts of the body. The condition improved in the summer and was aggravated after ingestion of eggs. No evidence as to mycotic infection was obtainable. The history was elicited through the questionnaire only.

The diagnosis was allergic prurigo of Besnier and Rasch.

The Wassermann reaction, patch tests with substances likely to cause eczema and tests with protein extracts and with albumin were negative.

There was no dermographism.

The results of other tests are given in the tabulation.

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive (wheal, 11 by 13 mm.; reflex erythema, 50 by 60 mm.; pseudopods, 2)<br>delayed reaction, negative |
| Scarification and patch test with trichophytin (1:1 dilution) | Negative |
| Trichophytin titer | $10^{-2}$ (wheal, 12 mm.; reflex erythema, 50 mm.) |
| Prausnitz-Küstner reaction | 10 experiments, negative. |

CASE 8.—E. B., a youth aged 18, a laborer, stated that his father suffered from asthma and that one sister had allergic eczema (allergic prurigo). Since the age of 3 years the patient had had a pruriginous cutaneous condition localized to the corners of the mouth and the flexures of the elbow and knees. In the summer of 1935 epidermatophytosis localized to the interstices of the toes of the right foot developed. Treatment with ethyl para-oxybenzoate resulted in its disappearance.

The diagnosis was allergic prurigo of Besnier and Rasch.

The Wassermann test and patch tests with substances likely to cause eczema were negative. In 1935 a test with goose feather extract gave a 6 mm. reaction; in 1936 the reaction was negative.

| | |
|---|---|
| Test with trichophytin (0.1 cc. of 1:10 dilution intracutaneously) | Immediate reaction, positive. (wheal, 16 by 17 mm.; reflex erythema, 60 mm.; pseudopod, 1) delayed reaction, negative |

In the cases reported the term allergic prurigo of Besnier and Rasch refers to the clinical conception formulated by Rasch [21] in 1913, which marks off a part of Besnier's original prurigo group (*prurigo diasthésique*). The conception corresponds fairly closely to the more recent designations of flexural eczema, neurodermatitis and *spätexsudative Ekzematoide* (Rost), while Sabouraud's asthmatic prurigo must be construed as an even more limited conception.

## COMMENT

*Specificity of the Reaction.*—Before discussing the similarities found in the cases reported it must be determined: (1) whether the reaction is specific in each case, i. e., due to a component present in the fungus or produced by it, and (2) whether the reaction is actually due to hypersensitivity. It is necessary, therefore, to make sure that the antigen has no primarily toxic effect. Behring's trichophytin (operations no. 10) was used for the tests. It never produced immediate reactions in the control tests made on a number of normal persons. This control is essential owing to the fact that commercial trichophytin is frequently primarily toxic and thus causes both immediate reactions (generally very weak) and local necroses, probably on account of the foreign protein content in the culture medium.

It is then necessary to make sure that the patient is not hypersensitive to the culture medium, as has been observed occasionally in other intracutaneous tests, e. g., with Bang's allergen (W. Jadassohn,[22] Dubois and Sollier [23]). I had an opportunity of observing a patient who had a severe immediate reaction to commercial trichophytin (general reaction) but no reaction to an extract of fungi cultivated on Sabouraud's agar, while the scarification test revealed hypersensitivity to beef broth.

Like Sulzberger and Kerr,[11] I have performed control tests with horse flesh bouillon, beef broth, agar-agar, raw maltose, peptone, 0.5

21. Rasch, C.: Nord. med. ark. **11**:9, 1913.

22. Jadassohn, W.: Arch. f. Dermat. u. Syph. **156**:690, 1928; **164**:656, 1932.

23. Dubois, C., and Sollier, N.: Compt. rend Soc. de biol. **109**:359 (Feb. 12) 1932.

24. Footnote deleted.

per cent phenol and mold fungi, and I have never encountered a reaction. The foreign components in the commercial product being beyond control, control tests have also been made with an extract of E. interdigitale cultivated on Sabouraud's agar; this allowed the culture medium itself to be used for controlling. With this extract strong immediate reactions and negative reactions for the culture medium were obtained in all the persons subjected to examination.

Consequently, there seems to be no doubt that the immediate reaction is acutally due to a component of mycotic origin. The uniform results obtained by Tomlinsson [17] with kindred fungus extracts offer further confirmation of this theory. It is open to question, however, whether this component is identical with that which produces the delayed reaction in a normal person with a mycotic infection. Jadassohn and Schaaf [25] have demonstrated the presence of various components in trichophytin. In collating this with the intricate and not fully explained chemical composition of trichophytin, with the results of Jadassohn, Schaaf and Sulzberger's [26] experiments with dialysate indicating a hapten character, and with Dienes' [8] and Bosch, György and Witebsky's [9] experiments with components of albumin, one finds that everything suggests the possibility of compound antigen structure. However, the same component of trichophytin seems to be consumed in the immediate reaction and in the delayed reaction to trichophytin. This is plainly seen when experimental transmissions are made from patients with a strong immediate reaction to normal persons with a strong delayed reaction. When the immediate reaction in the skin of the person experimented on has subsided, the natural delayed reaction is considerably weaker or, in many cases, fails to appear at all. I shall revert to these observations, which may sometimes constitute a source of error. The fact that the delayed reaction usually fails to appear in patients with urticarial hypersensitivity is a further indication that the immediate and the delayed reaction have a common etiology and can be explained in a satisfactory manner by assuming that two different antibodies directed against the same antigen are present.

The following evidence of the specificity of the reaction has been obtained: 1. Reactions to culture mediums and disinfectants may be excluded (Sulzberger). 2. Reactions are the same for various kinds and mixtures of trichophytin (Tomlinsson). 3. The component producing the delayed reaction is also consumed (or destroyed) in the immediate reaction. 4. The reactions often appear separately, or, to put it more exactly, patients with urticarial hypersensitivity often have

25. Jadassohn, W., and Schaaf, F.: Klin. Wchnschr. **12**:1170 (July 29) 1933; Schweiz. med. Wchnschr. **65**:737 (Aug. 17) 1935.

26. Jadassohn, W.; Schaaf, F., and Sulzberger, M. B.: Klin. Wchnschr. **11**: 857 (May 14) 1932.

no delayed reactions (see Sulzberger and Kerr, however), even if the duration and intensity of the infection warrant expecting those reactions.

*Etiologic Resemblances.*—As there consequently seem to be legitimate grounds to consider anaphylactic hypersensitivity toward tricho-

TABLE 1.—*Relations Between Allergy to Trichophytin, Allergic Predisposition and Mycotic Infection*

| | Allergic Predisposition | | | Mycotic Infection | | |
|---|---|---|---|---|---|---|
| Author | Familial Predisposition | Allergic Symptoms | Protein Tests (38 Extracts) | Duration | Localization | Hematogen Spreading (Trichophytid) |
| Sulzberger and Kerr | ..... | ..... | ? (+ Penicillium glaucum) | Several years | Feet | + Hands |
| Wise and Sulzberger | ..... | Asthma; hay fever; allergic eczema | ..... | 2 years | Feet | + Hands |
| Ramirez | ..... | Rhinitis; conjunctivitis; asthma | ..... | 2 years | Feet | ..... |
| Goldsmith | ..... | ..... | ..... | 12 days | Hands | + (Erythema multiforme) |
| Tomlinsson | ..... | ..... | ..... | 5 years | Feet | + |
| Marcussen | | | | | | |
| Case 1 | ..... | Urticaria | ..... | 3 years | Right foot | Urticaria (+) or urticarial trichophytid |
| Case 2 | ..... | ..... | ..... | 15 years | Left foot | ..... |
| Case 3 | In a sister urticaria after lobster | Urticaria | + Goose feathers<br>+ Pollen of Avena elatosior<br>+ Pollen of Dactylis<br>+ Maize<br>+ Raspberry | 2 years | Left foot | Urticaria (+) or urticarial trichophytid |
| Case 4 | ..... | ..... | ..... | 3 weeks | Chin (Kerion) | + Exanthematic |
| Case 5 | In a sister urticaria after oranges | ..... | + Shrimps<br>+ Maize | 4 weeks | Left arm | ..... |
| Case 6 | + | Allergic eczema | + Lactalbumin<br>+ Lactoglobulin<br>+ Rice | A few weeks some years ago | Feet | + Formerly |
| Case 7 | + | Prurigo (Besnier and Rasch) | ..... | ..... | ..... | ..... |
| Case 8 | + | Prurigo (Besnier and Rasch) | + Goose feathers | A few weeks | Feet | ..... |

phytin as a particular form of allergy, I shall give a schematic arrangement of the cases described.

Table 1 shows (1) that allergic predisposition was found in 9 of 13 cases; (2) that intensive mycotic infection was present in 12 of 13 cases.

The dermal tests consisted of scarification with thirty-eight protein extracts (Baagø and Barfod) supplemented by tests with several mold

fungi. Details are given in the case records. In Sulzberger and Kerr's case the condition was classed as primarily allergic owing to the positive cutaneous reaction to Pencillium glaucum, which is perhaps too little to go on. In case 7, in which it was not possible to ascertain the presence of a mycotic infection, the history was elicited through the questionnaire only.

Without intending to draw any conclusion from these cases, the number of which is too limited and the selection of which too partial, I wish to call attention to the fact that the concurrence of the two factors, allergic predisposition and intensive mycotic infection, may well explain the appearance of the urticarial reaction to trichophytin. Fungi are now and then found circulating in the blood stream of a patient with trichophytids (Jessner, Falchi and Arzt-Fuhs). The probability that this is often the case is increased by the results of W. Jadassohn's and Sulzberger's experiments with guinea-pigs. Trichophytids were present in 8 of 13 cases, this indicating that intense sensitization was probably present in most of the cases. The way in which mycetes may be the origin of strong allergies has often been described; it has been shown experimentally by Storm van Leeuwen [27] and has been demonstrated in asthma by Hopkins, Benham and Kesten,[28] and particularly by Hansen [29] and by Berger and Hansen [30] (the last mentioned authors having pointed out the frequent monovalent sensitization among other things). The possibility of mycotic eczemas causing sensitization has been emphasized by Hilgermann,[31] by Niethe,[32] and by the results of research made in recent years, e. g., by Brown [33] and by Balyeat,[34] who mentioned that such sensitization occurs rarely. Case 8 demonstrates that the allergy to trichophytin may alternate with other forms of allergy (compare Hansen and Nachmann [35] and Black.[36] In case 8 in this series the patient had a positive reaction to goose feathers and a negative reaction to trichophytin the

27. Storm van Leeuwen, W.: Allergic Diseases, Philadelphia, J. B. Lippincott Company, 1925.

28. Hopkins, J. S.; Benham, R. W., and Kesten, B. M.: Asthma Due to Fungus: Alternaria, J. A. M. A. **94**:6 (Jan. 4) 1930.

29. Hansen, K.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:204, 1928.

30. Berger, W., and Hansen, K.: Deutsches Arch. f. klin. Med. **173**:463, 1932.

31. Hilgermann: München. med. Wchnschr. **66**:702, 1921.

32. Niethe: Arch. f. Dermat. u. Syph. **153**:358, 1920.

33. Brown, G. T.: Ann. Int. Med. **6**:655, 1932.

34. Balyeat, R. M.; Stemen, T. R., and Taft, C. E.: J. Allergy **3**:227, 1932.

35. Hansen, K., and Nachmann, E.: Deutsches Arch. f. klin. Med. **177**:432, 1935.

36. Black, J. H.: J. Allergy **4**:24, 1932.

first time he was tested but a negative reaction to goose feathers and a positive immediate reaction to trichophytin when he attended the clinic again, a mycotic infection having developed in the meantime.

Finally, attention is called to the fact that 3 of the patients in this series were manifestly allergic, 1 having latent allergy while 2 had urticaria possibly of a mycotic nature. Similar conditions were present in the cases reported by the authors referred to.

*Appearance and Strength of the Immediate Reaction.*—The intradermal tests were made with a 1:10 dilution of Behring trichophytin. The appearance of the reaction tallied with other urticarial reactions in every respect. In case 2 in which the first injection was followed by violent general symptoms, only a control test with a 1:10,000 dilution of trichophytin was performed. In case 3 the reaction took a somewhat different course: an urticarial reaction lasting for about thirty-five minutes was followed by considerable infiltration and edema of the femur, the maximum point being reached after about two hours. The infiltration was still ascertainable after twenty-four hours, and thus it reminded one of Tezner's hyperergic immediate reaction. This patient had an exceptionally high reagin titer, which will be commented on separately.

*Scratch Reactions and Patch Tests.*—Strong reactions to scratch tests were observed in 3 patients, particularly in P. S. J. (case 2), who showed edema of the entire forearm besides a wheal measuring 33 mm. The edema disappeared after three hours. No patients showed epidermal reactions.

*General Reaction.*—P. S. J. (case 2) displayed most alarming symptoms after the intracutaneous test, i. e., asthma, generalized urticaria, facial edema and collapse. Similar manifestations have been reported by Ramirez and by Sulzberger and Wise, and though they occur rarely, a call for caution in the use of strong solutions of trichophytin at the first injection is warranted (Templeton).

*Nonappearance of the Delayed Reaction.*—Only 1 of the 8 patients displayed a delayed reaction. This patient (case 4) had kerion and exanthematic trichophytids and was given an injection of trichophytin when the kerion was at its acme a few days after the eruption of the trichophytids. This delayed reaction was of exactly the same appearance as the trichophytids (fig. 2) and occurred about seventy-two hours after the injection; peeling occurred and the eruption disappeared in about fourteen days. Imitation of a trichophytid by the trichophytin reaction is a familiar phenomenon (Bloch), but in this case the time and the development rather suggested a provoked tricho-

phytid (Peck,[37] Pautrier and Ullmo[38]), which often groups itself around the site of the injection. The exanthematic form has often been observed (Rasch, Williams, Jesionek, Matras[39]).

No delayed reaction appeared in Tomlinsson's patient, while Sulzberger and Kerr's patient showed a perfectly normal delayed reaction. Hence, it is a fact that the delayed reaction does not appear in some persons with urticarial hypersensivity, however much one would expect it in view of the intensity of the infection. When repeated hourly injections are given on the same site a local desensitization develops, but even then the delayed reaction fails to appear. This nonappearance cannot, then, be accounted for by local consumption of the allergen; it must be due to the fact that persons with urticarial hypersensitivity are unable to produce delayed reactions.

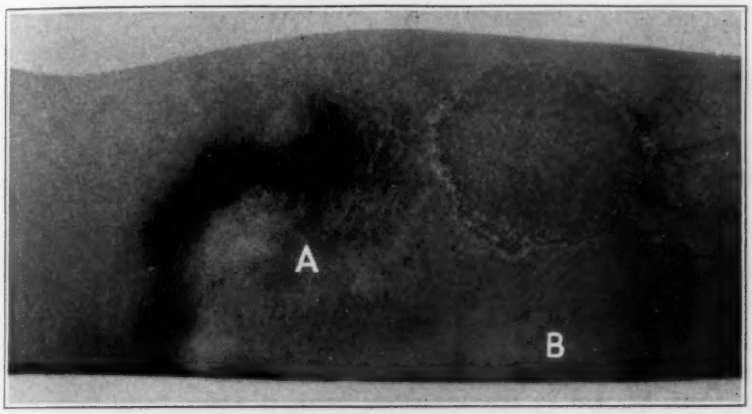


Fig. 2.—*A*, immediate reaction which has almost disappeared; *B*, imitative delayed reaction or provoked exanthematic trichophytid.

This agrees with the results of Tezner's sensitization experiments and with the theory that there is a difference between the antibodies in persons with anaphylactic hypersensitivity (atopic) and those in parenterally sensitized normal persons. The fact that both forms of antibodies may be present in the same patient (Sulzberger and Kerr's case) is not inconsistent with this.

*Diagnostic Importance.*—In certain cases of mycosis of long duration, especially in those in which hematogenous spreading is present,

37. Peck, S. M.: Epidermophytosis of the Feet and Epidermophytids of the Hands: Clinical, Histologic, Cultural and Experimenal Studies, Arch. Dermat. & Syph. **22**:40 (July) 1930.

38. Pautrier, L. M., and Ullmo, A.: Bull. Soc. franç. de dermat et syph. **38**: 1382, 1931.

39. Matras, A.: Arch. f. Dermat. u. Syph. **163**:47; **164**:291, 1931.

there will thus be no delayed reaction but only the easily overlooked immediate reaction. This may explain the nonappearance of the reaction to trichophytin so often reported (Bloch, Matras, Williams), which seems to occur mostly in connection with extensive deep conditions of long duration. The immediate reaction therefore seems to offer certain practical possibilities for diagnosis.

*Experiments on Transmissibility.*—The transmissibility of the immediate reaction to trichophytin has been demonstrated by Sulzberger and Kerr [11] and confirmed by Tomlinsson [17] and Ramirez.[13] Experimental transmissions are of interest because they make it possible to bring about the occurrence of both the immediate and the delayed reaction in exactly the same part of the skin and to observe their interaction. As transmissibility varies considerably with the different serums, it was necessary to lay down certain conditions for the experiments, which I shall mention briefly.

The technic adopted for the experimental transmissions was the common one. Sterile storage of the serum in a refrigerator for ninety-six hours was carried out to preclude any risk of infection (Zurhelle and Strempel [40]). The Wassermann reaction was controlled. Hermetically sealed ampules were used when the period of storage was prolonged. Serum from patients who had a negative reaction to trichophytin was employed for the controls, though this was doubtless unnecessary, as the common infectious hypersensitivity to trichophytin does not seem to be transmissible (Sulzberger, Tomlinsson). I have checked this by transmissions from a number of patients with particularly intense delayed reactions and trichophytids, the results of which were invariably negative. Transmissibility has, however, been reported in a few cases (Lehner and Rajka [41]); therefore, it was not considered advisable to disregard this factor. The site of the experiments was the volar surface of the forearm. The controls were the usual ones:

| | First day | Second day |
|---|---|---|
| Site of experiment | Serum from an allergic person | Trichophytin |
| Control 1 | Serum from an allergic person | 5% phenol, saline solution |
| Control 2 | Control serum | 5% phenol, saline solution |
| Control 3 | Control serum | Trichophytin |

The results have been determined by the technic of Berger and Hansen.[42] Berger and Hansen and P. W. Schmidt [43] have also provided a criterion whereby to judge a positive reaction. A minimum average diameter of 15 mm. was fixed. (Controls were absolutely nega-

40. Zurhelle, E., and Strempel, R.: Arch. f. Dermat. u. Syph. **153**:219, 1927.
41. Lehner, I., and Rajka, E.: Arch. f. Dermat. u. Syph. **161**:69, 1930.
42. Berger, W., and Hansen, K.: Deutsches Arch. f. klin. Med. **170**:499, 1931.
43. Schmidt, P. W.: Arch. f. Dermat. u. Syph. **161**:152, 1930.

tive.) No doubt many experiments in which a weak positive result was obtained have thereby been eliminated, but the preclusion of misconceptions attaching to subjective judgment and to the somewhat unsymmetrical placing has been attained. The development of a reflex zone was considered a definite condition for positivity. Generally speaking, the reactions were strong.

The strength of the antigen has been a more difficult matter. According to Bloch, Labouchère and Schaaf [44] and to Goodman and Marks,[45] the trichophytin allergen must be considered to be independent of protein substances, which debarred the use of chemical standardization (Hubbard and Osgood [46]). There are many indications on the whole that the trichophytin allergen is not a protein substance, e. g., Jadassohn [22] and Schaaf's experiments with dialyzed trichophytin, the great resistance of trichophytin to heating and its activity in extreme dilutions (case 3). But, as Harkavy and Witebsky [47] have shown, the titration of the strength of the allergen contributes in a high degree to throw light on experiments on transmissibility. The procedure adopted, then, was to make a number of dilutions on the basis of a definite amount of trichophytin and use them in all the experiments, constantly controlling their strength by weekly tests on several patients with the weakest dilution still active (trichophytin titer). During the period of experiment the dilutions proved to be of an absolutely constant strength. This indicates, too (considering the fact that several patients were constantly subjected to the tests), that the degree of hypersensitivity within a certain short period is constant. As certain patients reacted to exceptionally strong dilutions, a rather sensitive standardization yielding comparable results—even if it constitutes no absolute standard—is involved here. The solutions of antigens were made by shaking them in a mechanical shaker for several hours: 10 Gm. of antigen and 90 Gm. of dilution fluid (weighed out) were used for each stage of dilution (1:10). Unused receptacles were selected for each shaking. Two groups of dilutions in physiologic solution of sodium chloride and Coca's fluid, respectively, were produced.[48] Only slight deviations were found in the reactions to the two groups of dilutions. In determining the reagin titer it was necessary to begin with physiologic

44. Bloch, B.; Labouchère, A., and Schaaf, F.: Arch. f. Dermat. u. Syph. **148**:413, 1925.

45. Goodman, H., and Marks, I.: Reaction to Trichoyhytin Compared with Reactions to Other Bacterial Products, Arch. Dermat. & Syph. **31**:819 (June) 1935.

46. Hubbard, R. S., and Osgood, H.: J. Allergy **6**:231, 1935.

47. Harkavy, J., and Witebsky, E.: J. Allergy **6**:437, 1935.

48. The solutions of allergen were made in cooperation with P. C. T. Barfod, Chief Chemist.

solution of sodium chloride as a control and then proceed from weak dilutions to strong ones, for the allergen proved resistant, being unaffected by boiling for six hours and being destroyed only by 25 per cent sulfuric acid. Without intending to enlarge on this subject, I should like to call attention to the resemblance of the chemical properties of the allergen to the purified trichophytin produced by Bloch, Labouchère and Schaaf,[44] and also to its resemblance to the ascaris antigen (W. Jadassohn) as observed by Tomlinsson.

In table 2 the cases are enumerated according to the trichophytin titer found. It will be observed that the percentage of "takes" is in direct ratio with the allergen titer, as pointed out by Smyth and Bain [49] among others. It also appears from the table that positive transmissibility is not obtained at all with patients whose reagin titer is below 1 : 100. This confirms the frequent statements to the effect

TABLE 2.—*Correlation of Allergen Titer and Percentage of Prausnitz-Küstner Reaction "Takes"*

| Case | Allergen Titer | Prausnitz-Küstner Reaction | | | |
|---|---|---|---|---|---|
| | | Negative | Positive | Percentage of "Takes" | Total |
| 3 | $10^{-18}$ | 0 | 20 | 100 | 20 |
| 2 | $10^{-5}$ | 6 | 23 | 79 | 29 |
| 1 | $10^{-4}$ | 25 | 19 | 43 | 44 |
| 5 | $10^{-3}$ | 7 | 1 | 12 | 8 |
| 4 | $10^{-2}$ | 14 | 0 | 0 | 14 |
| 6 | $10^{-2}$ | 10 | 0 | 0 | 10 |
| 7 | $10^{-2}$ | 10 | 0 | 0 | 10 |
| 8 | $10^{-2}$ | 10 | 0 | 0 | 10 |
| Total | | 82 | 63 | | 145 |

that the Prausnitz-Küstner reaction fails to appear in some persons who have positive reactions to cutaneous tests (de Besche,[50] Markin,[51] Smyth and Bain,[49] Williams and Carpenter [52]) and accounts for the observation in a perfectly simple manner. Taken all in all the positive Prausnitz-Küstner reaction appears to require certain quantitative conditions. The paramount importance of the reagin titer has been demonstrated best by Walzer and by Salén.[53] When weaker reagin titers are employed special conditions in the skin of normal patients seem to play a part too. A test with 0.1 cc. of a 1 : 1,000 dilution of histamine was carried out and the reaction measured by the technic of Berger and

49. Smyth, F. S., and Bain, K.: J. Allergy **2**:181, 1931.

50. de Besche, A.: Acta path. et microbiol. Scandinav. **6**:114, 1929; Nord. med. tidskr. **9**:916 (June 1) 1935.

51. Markin, L. E.: J. Allergy **2**:285, 1931.

52. Williams, C. M., and Carpenter, C. C.: Trichophytin in Diagnosis, Arch. Dermat. & Syph. **25**:847 (May) 1932.

53. Salén, E. B.: Acta med. Scandinav. **78**:194, 1932.

Hansen on 145 normal persons. The variation graphs indicating the extent of the wheal and of the erythema in patients with positive and negative Prausnitz-Küstner reactions, respectively, were found to be perfectly identical. This conflicts with experiments made by Carey and Gay [54] and others, but the material is not sufficiently extensive to allow definite conclusions.

*Relation of the Immediate to the Delayed Reaction.*—In the course of his experiments on transmissibility Sulzberger observed severe delayed reactions in three normal persons to whose skin he failed to effect transmissions. He consequently raised the question as to whether successive desaturation by circulating mycetes of the reagin injected might have taken place. I have made control tests on 85 normal persons, 50 of whom had intense delayed reactions to trichophytin. Only serum from the 3 patients with a high percentage of "takes" was used for this purpose.

Among 50 normal persons with a positive reaction to trichophytin, 31 had a positive and 19 had a negative Prausnitz-Küstner reaction, and among 35 normal persons with a negative reaction to trichophytin 21 had a positive and 14 had a negative Prausnitz-Küstner reaction.

The only inference to be drawn from this is that the transmissibility is the same for patients with positive and for those with negative reactions to trichophytin. This is no reply to Sulzberger's question, as none of the patients had clinical mycosis. The outcome of experimental transmissions to patients with trichophytids would be valuable also in regard to the question of the pathogenesis of the trichophytid.

Finally, I shall give a short summary of the circumstances attending the course of the delayed reaction and the immediate reaction in the same person's skin.

Figures 3 and 4 show the clinical picture on the first day of the experiment (immediate reaction on the site subjected to the experiment) and on the third day (nonappearance of delayed reaction on the site, with normal delayed reaction corresponding to the reaction in control 3). As a guide to the quantitative factors, the data on a series of experiments made with serum from I. B. (case 3) are given (only the essentials have been included).

Table 3 shows that the course of the immediate reaction induces a diminution of the delayed reaction or results in nonappearance of the latter. This phenomenon could be explained in different ways, viz., by (1) diffusion of the trichophytin; (2) local desensitization, (3) consumption of the same antigen component as that evoking delayed reaction. That disappearance by spreading plays a certain minor part was ascertained by experimental transmissions of serum from a patient

54. Carey, T. N., and Gay, L. N.: J. Allergy **5**:488, 1934.

with hypersensitivity to goose feathers in which equal parts of extract of goose feathers and trichophytin were used as allergen. An intense immediate reaction to goose feathers appeared and was followed by a

Fig. 3.—Immediate Prausnitz-Küstner reaction.

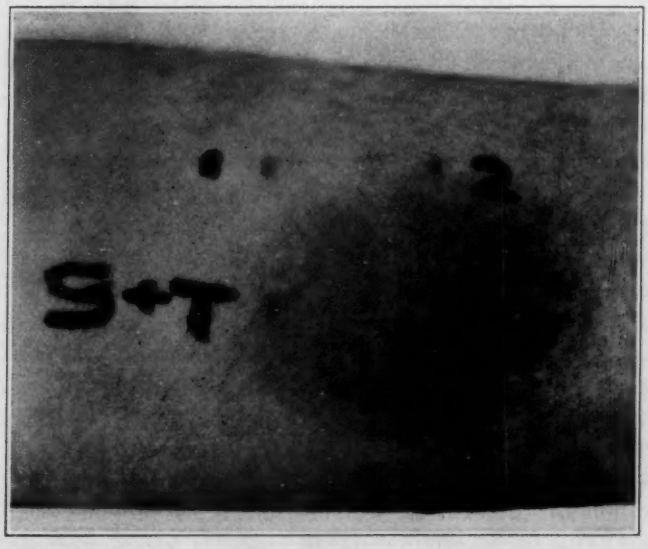


Fig. 4.—Nonappearance of delayed reaction corresponding to the site of the experiment. Normal delayed reaction corresponding to reaction in control 3.

delayed reaction to trichophytin, which was larger and less infiltrated than the control reaction. Incidentally, there is absolute mutual specificity for the hypersensitivity to trichophytin and goose feathers; I

had an opportunity of testing this in Prausnitz-Küstner experiments with serum from I. B. (case 3), which gave reactions with both. Complete desensitization with goose feather extract had no effect on the immediate reaction to trichophytin.

That local desensitization has no effect was proved by reinjection of trichophytin made after the disappearance of the immediate reaction in Prausnitz-Küstner experiments on patients with a normal delayed reaction. A natural delayed reaction developed in such a case.

The only possibility left seems to be, then, that the same antigen component produces the immediate reaction and the delayed reaction. As previously mentioned, this is in harmony with the results of Tezner's experiments on sensitization of normal persons and of persons with

TABLE 3.—*The Influence of the Immediate on the Delayed Reaction*

| | First Day of Experiment Immediate Reaction | | Third Day of Experiment Delayed Reaction | |
|---|---|---|---|---|
| Subject of Experiment | Size of Reaction to Serum from Allergic Person and Trichophytin | Size of Reaction to Serum from Normal Person and Trichophytin (Control 3) | Size of Reaction to Serum from Allergic Person and Trichophytin | Size of Reaction to Serum from Normal Person and Trichophytin (Control 3) |
| F. L. | 25 × 22 mm. | ..... | 10 × 12 mm. | 13 × 16 mm. |
| E. F. | 21 × 25 mm. | ..... | ..... | 14 × 14 mm. |
| A. R. | 40 × 25 mm. | ..... | 10 mm. | 18 × 20 mm. |
| A. K. | 26 × 26 mm. | ..... | ..... | 12 × 12 mm. |
| H. F. | 25 × 24 mm. | ..... | 9 × 12 mm. | 15 × 20 mm. |
| K. C. | 25 × 26 mm. | ..... | ..... | 7 × 7 mm. |
| O. I. | 19 × 20 mm. | ..... | ..... | 10 × 12 mm. |
| P. M. | 22 × 14 mm. | ..... | 5 × 6 mm. | 20 × 23 mm. |
| E. H. | 18 × 25 mm. | ..... | ..... | 17 × 21 mm. |
| A. A. | 20 × 20 mm. | ..... | 5 × 8 mm. | 12 × 12 mm. |
| E. E. | 21 × 21 mm. | 12 × 15 mm. | 15 × 17 mm. | 23 × 23 mm. |
| E. O. | 21 × 21 mm. | 10 × 11 mm. | 5 × 6 mm. | 35 × 40 mm. |
| M. V. | 21 × 22 mm. | ..... | ..... | 10 × 10 mm. |
| P. O. | 25 × 35 mm. | 10 × 9 mm. | 7 × 11 mm. | 25 × 25 mm. |
| I. H. | 20 × 21 mm. | ..... | ..... | 9 × 9 mm. |
| Average | 23.2 mm. | > 2.2 mm. | 4.9 mm. | < 16.7 mm. |

allergic predisposition, if mycotic infection is compared with parenteral sensitization.

## CONCLUSION

Mycotic infection seems capable of giving rise to the formation of two different antibodies, one of which circulates in allergically predisposed persons while the other is a sessile antibody that may be present in any person with mycotic infection but is often absent in an allergically predisposed subject. Both antibodies are directed against the same antigen component and occur in the same person in certain cases (Sulzberger and Kerr's case). This relationship of the two reactions to each other is in exact correspondence with the relationship demonstrated by Tezner in experiments on immunization with albumin, pollen and ascaris antigen. In view of the fact that the immediate reaction is specific, that it is induced by the same antigen component as the

delayed reaction and that it seems, like the latter, to be induced by mycotic infection, it must also be supposed to possess the same diagnostic value.

SUMMARY

Eight cases of urticarial reactions to trichophytin are described.

The reaction proved to be specific in all the cases reported.

The probability that allergic predisposition and prolonged deep mycosis, often attended by hematogenous spreading, are important etiologic factors is shown on the basis of the case reports.

By means of experimental transmissions to persons with delayed reaction according to the Prausnitz-Küstner technic it is demonstrated that the immediate and the delayed reaction consume the same antigen component.

The two reactions seem to be of the same diagnostic value, but the immediate reaction is likely to lead to errors, being easily overlooked and possibly depending in certain cases on primary toxicity of the trichophytin or on hypersensitivity toward the components of the culture mediums on the part of the person tested.

Quantitative aspects of Prausnitz-Küstner's experiments are elucidated by titration of the degree of hypersensitivity.

# THE PATHOGENESIS OF NONCASEATING TUBERCULOSIS OF THE SKIN AND LYMPH GLANDS

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AND
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Recent observations of developments in the life history of the tubercle bacillus [1] have afforded opportunity to reinterpret perhaps the traditional bacteriologic observations in noncaseating tuberculosis both in the skin and in the lymph nodes. The rather atypical clinical and pathologic features of conditions such as Boeck's sarcoid have always lacked any satisfactory explanation from the standpoint of pathogenesis. We shall present the clinical and clinicopathologic aspects of a human case and give an elaboration of the bacteriologic inquiry and its bearing on pathogenesis.

## REPORT OF A CASE

J. J., a Negro aged 18, consulted us because of lesions on the forehead, cheeks, neck, arms, back, abdomen, thighs and legs. The patient made the statement that eight years previously he had sustained a fall which resulted in a laceration of his forehead; this when healed left a painless mass the size of a hazelnut at the site of injury. One year before he consulted us, the patient noticed the appearance on his face of firm pinhead-sized subcutaneous brownish red lesions. At first the lesions were round and smooth, but later they reached the size of a large pea, showed a central necrotic plugging and then healed, leaving a soft depressed brownish scar, which in some instances was covered by fine scales (fig. 1).

Occasionally the lesions grouped, forming a nodular, rosette-like mass which tended to ulcerate early. In the submaxillary region the lesions were larger and firmer and presented a keloidal appearance. None of the lesions was painful. Those appearing on the upper parts of the arms consisted of firm elevated nodular dense subcutaneous masses varying in size from that of a small to that of a large

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From the Institute of Pathology (Dr. Mellon) and the Department of Dermatology (Dr. Beinhauer) of the Western Pennsylvania Hospital.

1. (*a*) Mellon, R. R., and Fisher, L. W.: New Studies on Filtrability of Pure Cultures of Tubercle Group of Micro-Organisms, J. Infect. Dis. **51**:117, 1932. (*b*) Mellon, R. R.: The Newer Biology of the Tubercle Bacillus: Its Variability, Filtrability, and Life-Cycle Changes; in Goldberg, B.: Clinical Tuberculosis, Philadelphia, F. A. Davis Company, 1935, chap. 2. (*c*) Mellon, R. R.; Richardson, Ruth D., and Fisher, L. W.: Further Studies on the Life Cycle of the Avian Tubercle Bacillus, Proc. Soc. Exper. Biol. & Med. **30**:80, 1932. (*d*) Miller, Franklin: The Induced Development of Non-Acid-Fast Forms of Bacillus Tuberculosis and Other Mycobacteria, J. Exper. Med. **56**:411, 1932.

finger-nail. No ulceration was present, and the lesions underwent spontaneous involution, leaving atrophic soft brownish scars. Similar lesions were scattered over the flanks, the back and the abdomen.

To the left of the umbilicus there was a dime-sized plaque consisting of discrete pinhead-sized firm follicular and keratotic reddish brown scaly papules with slightly flat tops (fig. 2). The legs presented a symmetrical eruption involving for the most part the anterior and lateral surfaces and consisting of a series of recent pea-sized papulonecrotic lesions moderately inflamed and intermingled with numerous depressed scars of similar size. In some places the tendency to group-

Fig. 1.—Noncaseating nodules in the skin.

ing was apparent, the lesions forming elevated and flattened dime-sized plaques which healed, without ulceration, leaving soft depressed scars. A few keloid-like lesions were present; they were firmer than the others, were more flattened and underwent involution, leaving a depressed scar in the center surrounded by a periphery of active nodular lesions.

The lymph glands were generally enlarged. The posterior cervical chain presented a firm enlargement the size of a small pea. In the epitrochlear regions a distinct chain of firm painless nodes the size of large marbles was present. The inguinal and femoral glands were much larger, individually reaching the size of a hazelnut, and were matted and fused, giving the clinical appearance of one gland the size of a small orange.

The palms were not involved, but the soles revealed numerous discrete papulonecrotic lesions which left deeply pigmented scars. The bursae over the anterior aspects of the wrists were enlarged and fluctuating, giving the sensation of containing fluid. Both knees presented a more marked bursitis of a fusiform appearance, and pain could be elicited by pressure. The pupils were equal and reacted normally. The teeth were sound. The tonsils were deeply embedded, submerged and pale. The sinuses transilluminated well. The nose and ears were normal.

The chest was thin walled and had a normal contour anteriorly. Definite dulness was noted in both supraclavicular and infraclavicular areas; it was more marked on the right and extended downward to the third costal interspace. A small area of flatness was noted in the right axilla. Posteriorly the impairment was noticed only at the apexes. No friction or râles were heard, but a definite harshness was present over involved areas. The heart was normal in size, and a harsh systolic murmur was transmitted to the third interspace in the left midclavicular line. The abdomen was normal. The reflexes were normal. The

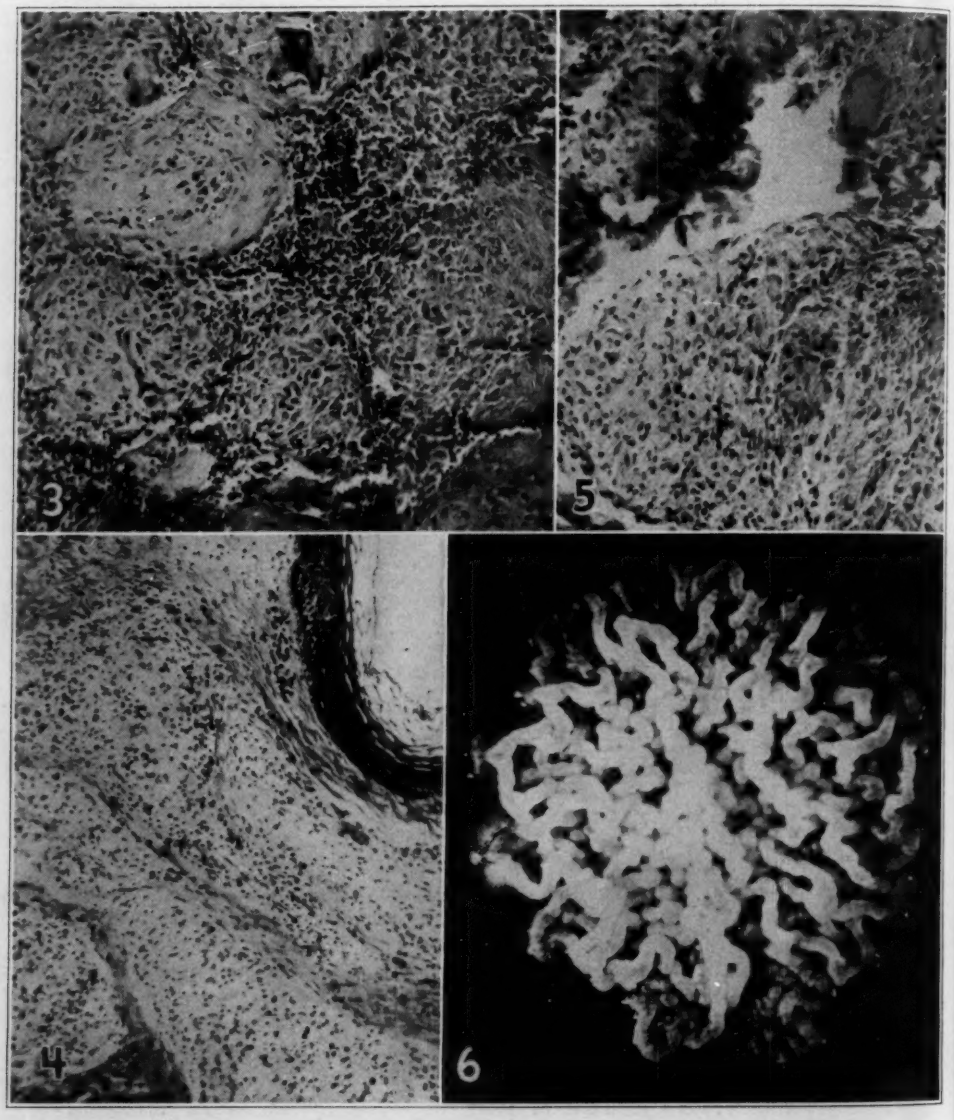
Fig. 2.—Minute papular lesion on the skin of the abdomen.

prostate was soft and even and showed no evidence of pathologic changes. There was no elevation of temperature at any time, and the pulse rate and respiratory rate were normal.

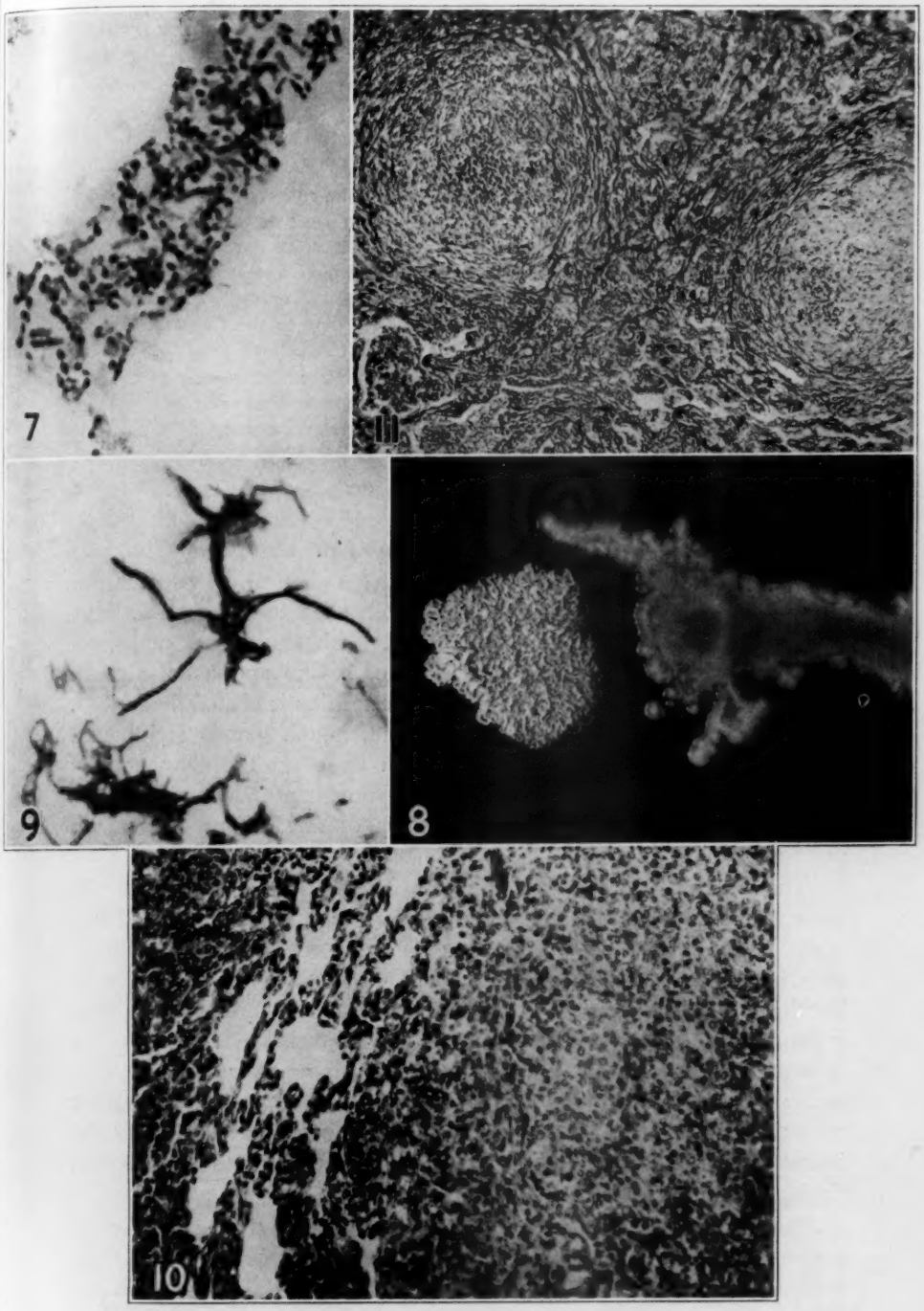
*Laboratory Examinations.*—The urine contained a trace of albumin; the specific gravity was 1.015; many hyaline and granular casts were seen, and there were from 18 to 20 white blood cells per high power field. The Wassermann and Kahn reactions were negative. The red blood cell count was 4,340,000; the white blood cell count, 8,000, and the hemoglobin content, 85 per cent. The differential cell count revealed 60 per cent polymorphonuclears, 16 per cent eosinophils, 14 per cent transitionals and large mononuclears and 10 per cent small lymphocytes.

Tests with 1:1,000 dilutions of avian, of bovine and of human tuberculin gave negative results. Repeated examinations of the sputum showed no tubercle bacilli. Cultures of the blood gave negative results. Prostatic smears showed no gram-negative intracellular diplococci.

*Roentgen Examination.*—Roentgen examination of the chest revealed a slight increase in the width of the mediastinal shadow at the level of the aortic arch. This was not the shadow of a blood vessel but was probably due to enlarged glands. There was a peribronchial infiltration in the apical regions, and both hilar shadows




Figs. 3 to 6.—Figure 3 shows early hyalinization of epithelioid noncaseating tubercles of a lymph gland. Note atypical Langhans giant cells; × 136. In figure 4 are subcutaneous lesions similar to those shown in figure 3, but with a tendency toward fibroblastic proliferation instead of hyalinization; × 100. Figure 5 shows subcutaneous lesions similar to those shown in figure 4, the lesions being sarcoid in type but with typical Langhans giant cells; × 160. Figure 6 shows the critical rough colony on blood agar; × 18.




Figs. 7 to 11.—Figure 7 shows the diphtheroid cells (sporoid culture), filled with acid-fast granules; × 1,350. Figure 8 shows the smooth sporoid culture (fig. 7) to the right. At the left is the critical rough colony; × 1.6. Figure 9 shows the branching filaments of the actinomyces-like structures; × 1,350. Figure 10 shows the pulmonary condition produced by the critical R form; × 140, and figure 11, that produced by the critical S form; × 120.

were enlarged. There was possibly a small amount of fluid at the base of the right lung. The entire picture was that of a low grade tuberculosis. Roentgenograms of both knees and of the right wrist showed no evidence of pathologic changes in the bones.

*Pathologic Examination.*—Lymph Node: Nearly the entire section was occupied by well defined epithelioid tubercles, separated by remnants of lymphoid tissue and thick strands of hyaline collagenous tissue. The tubercles were associated with multinucleated Langhans' cells, two or more of which appeared often in one tubercle. Caseous necrosis was not present, although the epithelioid cells showed marked hyaline degeneration. Sections stained according to the Cooper modification of the Ziehl-Neelsen technic revealed no acid-fast structures (fig. 3).

Skin: The epidermis was moderately hyperkeratotic, and flattening of the rete pegs was noted. The corium contained epithelioid tubercles similar to those present in the lymph node. An atypical feature of these tubercles was the almost complete absence of a peripheral zone of lymphocytes (figs. 4 and 5).

### BACTERIOLOGIC INQUIRY AND ITS BEARING ON PATHOGENESIS

Both on clinical and bacteriologic grounds the observations in cases such as that reported are often strangely paradoxical. For example, the clinical course, though prolonged, is relatively benign, in the sense that the patient is afebrile, the general state of health is good and there is anergy to the tuberculins from human, bovine and avian strains. However, it often happens that unless the condition is abated the lesions, which for so long are limited to the skin, lymph glands and bones, eventually extend to the lungs. In such an event the characteristic clinical signs, which have been lacking, assume a prominent place, and the patient thereafter takes on the status of any other patient with pulmonary tuberculosis.

The bacteriologic paradox consists in the fact that despite the presence—often in considerable numbers—of pleomorphic acid-fast bacilli in the stained sections of the glands, the results of both cultural experiments and inoculation of animals are negative for the tubercle bacillus. We used various culture mediums and experimental animals in unsuccessful attempts to confirm this tinctorial evidence for the presence of the tubercle bacillus so suggestively apparent in pathologic sections of tissue. Both cultures and inoculations have been rather exhaustive with the scant material which has come to hand. For the inoculations we have used, in addition to rabbits and guinea-pigs, chickens, mice and monkeys.

But despite the negative results of cultures for the tubercle bacillus per se, Schaumann [2] has pointed out that one may isolate at times from the lesions a certain nonacid-fast or partially acid-fast flora that has previously been regarded as consisting of secondary invaders. This has also been our experience. On the other hand, the organisms are of a

2. Schaumann, J.: Benign Lymphogranuloma and Its Cutaneous Manifestations, Brit. J. Dermat. **36**:515, 1924.

type that has suggested their being considered as nonpathogenic dissociants of the virulent tubercle bacillus; but as only within recent years has it been shown that such organisms are capable of being redissociated into the virulent tubercle bacillus, little support for the contention of previous observers has been at hand. The literature reviewing these studies has been collated in a recent paper by Miller.[1d]

The organisms to which we refer are actinomyces-like forms, diphtheroid bacilli with acid-fast granules, and coccoid organisms, sometimes with and sometimes without acid-fast granules. A few years ago there was published from this laboratory a preliminary study dealing with the life cycle of the tubercle bacillus,[1c] which included as quasi-stabilized stages two of the three types of organisms mentioned, namely, the coccus form and the diphtheroid form with acid-fast granules. In addition, it included a semisaprophytic acid-fast cyclostage, which was dissociated experimentally from the diphtheroid forms containing the sporelike acid-fast granules. This acid-fast culture, which we shall call the critical rough form (fig. 6), has also been shown to be a direct dissociant of the virulent S culture phase of the tubercle bacillus.[3]

In explanation of the diagram (fig. 12) we may say that stage I represents the virulent smooth colony, or S form, of the avian tubercle bacillus. Stage II represents a nonacid-fast but gram-positive granular stage which is reminiscent of the granules of Much and which in our hands was capable of passing through a Berkefeld filter. We refer to organisms in that stage as filtrable gonidia. These sporelike forms are capable under appropriate conditions of germinating either into stage III or into stage V. The former is a nonacid-fast diplococcus, and the latter is a diphtheroid bacillus, which because of the large acid-fast spore-like granules it contains has been designated a sporoid form. Rather characteristically, an appreciable portion of the whole bacillus seems to be made up of this large rather acid-fast granule (fig. 7), and it is from this that there appears to germinate stage VI.

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3. It is now well known that practically all bacteria exist in at least two phases: (1) a smooth colony (S), frequently virulent; and (2) rough colonies (R) of varying grades, which are likely to be avirulent or of lowered virulence. Yet, such associations of colony form and function are far from constant. In fact, the bacteriologic aspects of this study show that the S and R colony patterns not only are far from adequate to include the data here reported but are by no means constant as far as their virulence implications are concerned. Because these studies have such a pertinent bearing on the type of tuberculosis which we have to consider here, we have inserted the diagrammatic orientation of the cyclic relations of the tubercle bacillus in the paper referred to[1c] in addition to giving some of the high lights which have been developed since that time and are now in course of publication in extenso. Meanwhile, a fair perspective of its scope may be gained from a general review which we have made of the newer biology of the tubercle bacillus.[1b]

The colonies of stage VI are extremely rough (fig. 6 and fig. 8, left), in contrast to those of the smooth sporoid (fig. 8, right). This critical rough form, so called, is not to be confused with the conventional R forms of the tubercle bacillus described by Kahn and Schwarzkopf [4]—at least, if the strain sent us by Kahn may be considered typical. For culturally and in other ways their strains seem to occupy an intermediate position between our critical rough and the virulent S form. In all likelihood there are other intermediate forms, located perhaps at other segments of the cycle, an example of which is the actinomyces-like culture phase isolated in the case reported here (fig. 9). In this scheme it would occupy a place between stages V and VI. The granules of Much are, of course, classic structures of the tubercle

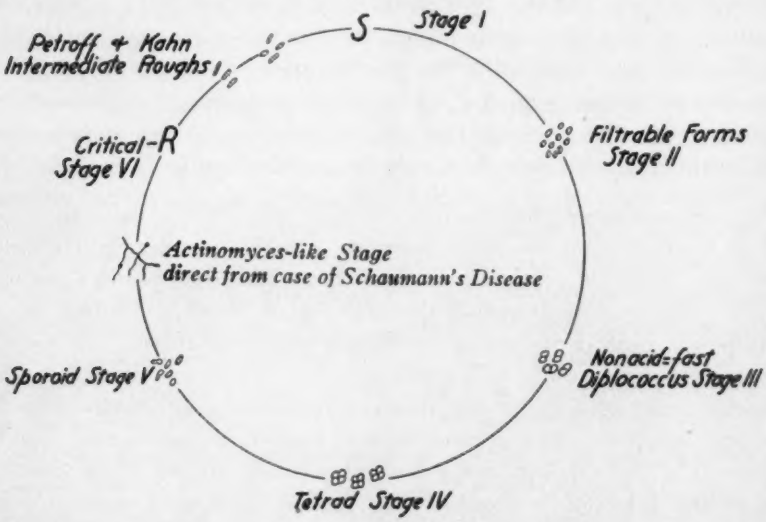


Fig. 12.—Diagrammatic orientation of the cyclic relations of the tubercle bacillus.

bacillus, while part of the nonacid-fast dissociants included in this cycle have been observed by others for the past thirty years. But, as we have indicated, final proof of such a relation must depend on their retransformation into the acid-fast tubercle bacillus. Since recent studies have made this a reality for us, the integration of all these culture phases by a single unifying conception now becomes possible. This conception is diagrammatically depicted in the dissociation cycle (fig. 12).

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4. Kahn, Morton C., and Schwarzkopf, H.: Single-Cell Dissociation of Acid Fast Bacteria: Mycobacterium of Avian Tuberculosis; Mycobacterium of "Rat Leprosy," J. Bact. **25**:157, 1933. Petroff, S. A., and Steenken, W.: Biological Studies of the Tubercle Bacillus: Instability of the Organism-Microbic Dissociation, J. Exper. Med. **51**:831, 1930.

## RELATION OF THE DISSOCIATION CYCLE TO THE BACTERIOLOGIC CHARACTERISTICS OF THE NONCASEATING TUBERCLE

The relationship just postulated focuses about the consideration that the nonacid-fast forms cultured from this type of tuberculosis are strikingly similar to those experimentally dissociated from the virulent tubercle bacillus itself, which are now known to be capable of eventually reverting to this organism, often by way of the critical R form to which we have referred. Yet in order to prove more than mere analogy, it is necessary to take at least one nonacid-fast culture isolated in an actual case of this type of tuberculosis and to dissociate it experimentally into a culture stage that can be recognized as falling in the cycle of the tubercle bacillus.

To make a long story short, that is exactly what we have accomplished in the clinical case the salient clinical features of which are included in this report. We elected to culture material from as young a lesion as possible for the following reasons: We were proceeding on the working hypothesis that the initial infective agent in cases of this kind is the semisaprophytic critical R form, which, although acid-fast itself, is possessed of the striking ability to dissociate more or less spontaneously into the nonacid-fast progeny already enumerated. As this occurred in the test tube, we thought that it might also take place in the patient, thus explaining why we were able to isolate conventionally only these relatively nonacid-fast and nonvirulent cultures from these lesions. But it seemed to us likely that the younger the lesion, the more nearly related would the nonacid-fast form be to the acid-fast form with which we assumed that the patient was infected originally; therefore, the greater would be the chance of reverting it into the acid-fast portion of the tubercle bacillus cycle. It may be remarked in passing that so great is the stability of these nonacid-fast cultural forms that their reversion to the acid-fast segment of the cycle is accomplished only with great difficulty.

A nodular lesion scarcely more than a week old was extirpated under aseptic technic from the face of the patient (fig. 1). Smears were seen to contain an occasional partially acid-fast thread or bacillary form. The material was seeded on various mediums, but the one which yielded the best results was a blood agar plate which after a week's incubation at 37 C. yielded a fair number of colonies of long branching thread forms which were amphophilic in their acid-fastness. That is to say, the single filament contained portions which were acid-fast and long stretches which were nonacid-fast (fig. 9). There were many bright red granules situated at intervals along the filaments. Transplants of these colonies to Dorset's egg medium produced similar colonies and showed adherence to the medium characteristic of cultures of the actinomyces. Acid-

fastness was maintained to a greater extent on this medium than on blood agar. Serial transplants on the latter medium resulted in an almost complete disappearance of the acid-fastness with the exception of granules and short segments of the filament.

After several weeks of transplantations on blood agar the actinomyces-like form was placed in the incubator at 37 C. for one week and was subsequently kept at the temperature of the laboratory for a week. At this time several small secondary colonies gradually extruded their way out of the growth; on closer examination these proved to have characteristics strikingly similar to the critical rough acid-fast form. It will be recalled that the latter first originated by dissociation from our nonacid-fast sporoid forms but at a later time was dissociated from the virulent S form of the tubercle bacillus itself. These secondary colonies proved indeed to be strictly acid-fast, and on transplantation they grew well both in Petragnani's medium and on blood agar in forty-eight hours. They not only were acid-fast but were inclined to be filamentous, with occasional branches, although this fungoid aspect was not nearly so definite as in the actinomyces-like culture derived from the patient. Moreover, subsequent detailed studies have shown that this acid-fast dissociant is culturally indistinguishable from those experimentally derived from both the avian and the human strain of the tubercle bacillus. In passing it may also be noted that several years after the strain had been isolated it dissociated into a sporoid (stage V), which further supports the orientation given the strain in figure 12.

It is noteworthy that no acid-fast organism could be cultivated directly from this material or from other specimens subsequently removed from this patient. The latter specimens were a subcutaneous nodule and a greatly enlarged inguinal gland. These were cultured both on blood agar and on a variety of tubercle bacillus mediums, including Dorset's egg medium. Acid-fast organisms were not detected in direct smears from either the nodule or the glandular material, and all the cultures failed to show any type of organism. It should be noted, however, that usually diphtheroids with acid-fast granules are isolated from such material (sporoid, stage V).

Moreover, relatively large quantities of the material were injected both into rabbits and into guinea-pigs, and the results were completely negative both from the standpoint of pathologic change produced and from that of isolation of any type of organism that could be even remotely referred to the tubercle bacillus cycle. Nevertheless, the structure of these lesions, as has been stated, was that of typical epithelioid tuberculosis (fig. 3), which at no place, however, showed the slightest sign of caseation.

By way of summary of the cultural results, it is seen that only from the very young lesion could organisms be cultivated; and then not any recognizable form of the tubercle bacillus per se resulted, but a partially acid-fast actinomyces-like form. But the latter's dissociation into a strictly acid-fast culture which was capable of being recognized as an integral part of the tubercle bacillus cycle realizes, we believe, the principal objective with which we started out. This concerns itself with the proof that certain of these nonacid-fast organisms were dissociant stages of the tubercle bacillus.

### IN VIVO DISSOCIATION OF THE ACID-FAST CRITICAL R STRAIN INTO NONACID-FAST DIPHTHEROIDS (SPOROID FORM)

It was our assumption in the beginning that highly susceptible skins are infected with an actual tubercle bacillus, but one the virulence and biochemical characters of which are so anomalous that only the epithelioid noncaseating type of lesion is produced. The hypothesis included also the early dissociation of this organism into either frankly nonacid-fast forms or partially acid-fast ones. The cultural characteristics naturally might be such as to make it difficult to recognize their connection with the tubercle bacillus proper.

Thus far the evidence supports the working hypothesis; but it would also be desirable to show experimentally that the acid-fast culture with which we presume the patient to have been infected originally is capable of causing noncaseating lesions of the same general type as those found in the patient, and also to show that it is capable of dissociating not only in vitro but also in vivo into one of the several types of nonacid-fast organisms which one recovers from the patient.

By way of anticipation we might say that both of these objectives have been realized experimentally in the following manner: It had previously been observed that tubercle bacilli of subinfective virulence frequently underwent exaltation of that virulence on serial transfer of the organism through the testicles of rabbits. While engaged in this procedure with the critical rough form obtained in the case in question, we were occasionally impressed by the fact that we were unable to cultivate the acid-fast organism from the testicle into which it had been injected, despite the profuse number of acid-fast organisms in the smear.

However, by seeding the material into broth containing serum we were able gradually to cultivate the nonacid-fast diphtheroid containing acid-fast granules, which was precisely the same in all respects as the organism from which we dissociated in the beginning our first critical R form of the tubercle bacillus. That is to say, there had occurred a loss of viability on the part of the injected acid-fast organism, which

in turn dissociated in the testicle of the animal into a nonacid-fast diphtheroid culture form of exactly the type observed in the majority of the patients with the condition under consideration,[5] which as we have previously remarked, has had the status of a secondary invader because of its hitherto undemonstrated connection with the tubercle bacillus of Koch.

### SPECIAL PATHOLOGIC FEATURES OF THE CRITICAL R STRAIN

The critical R form of the tubercle bacillus isolated in this and other cases can be dissociated at will into a smooth colony form, but only occasionally is it associated with the virulence of the normal S form of the tubercle bacillus. Despite the smoothness of their colonies, these nonvirulent dissociants of the critical R form are pathogenically much more closely related to it than to the virulent S form, as is shown by intratracheal inoculations of cultures of both critical R and critical S forms (figs. 10 and 11). The critical S form produces in the lungs of guinea-pigs a noncaseating epithelioid tubercle which involves the whole of one lung or of both lungs in massive fashion and which progresses to the tenth or twelfth day, after which it disappears gradually, almost all trace of it usually being lost at the end of six weeks.

The "whorl" form of tubercle that it evokes distinguishes its tissue reactions from those of the critical R form. It too produces a noncaseating epithelioid histologic response, but without the whorls. The epithelioid cells grow diffusely, often obliterating the alveolar spaces. It should be mentioned too that the initial tissue response to this organism in the lungs is generally of a pyogenic character, so that if the lungs are examined within from twenty-four to seventy-two hours one observes only polymorphonuclear infiltration of the alveolar spaces, such as would be expected in any type of pneumonia.

This cellular response is similar to that obtained when guinea-pigs are given intraperitoneal injections of the critical R form. A purulent omentitis develops, and although many of the guinea-pigs recover, a certain percentage of them eventually die. Yet the histopathologic picture of the lesions can never be identified as being specific for the tubercle bacillus. In fact, the polymorphonuclear response to organisms introduced by this route of inoculation is of course nonspecific. Only in the lung is the response of a type that makes it possible to suspect its tuberculous origin; and even here, the characteristic specific

5. Crawford, Stanley: Cutaneous Nodulodiscoid Tuberculosis of Anergic Type, with Development into Active (Allergic) Pulmonary Tuberculosis, Arch. Dermat. & Syph. **27**:766 (May) 1933.

caseation is always lacking, and if the critical R form instead of the S form is inoculated there is even a lack of the characteristic whorl formation of the tubercle.

From the standpoint, then, of anomalous lesions produced by the tubercle bacillus, it seems significant that the organism under consideration is acid-fast and capable of being experimentally dissociated from the tubercle bacillus but is apparently of such a biochemical make-up that it is not capable of causing the characteristic destruction of tissue which manifests itself in caseation of the tubercle once it is formed. And depending on the route of inoculation the tissue response may be so nonspecific as to make diagnosis of any form of tuberculosis impossible with the present criteria.

As a matter of fact, from the standpoint of pathology and medicine this is perhaps the most important connotation of the dissociation cycle of this organism. That is to say, the further the dissociation process recedes from the S form, the more nonspecific are the reactions elicited in the host. And when it finally grades into the nonacid-fast forms, practically the only response is a pyogenic one; and even with the acid-fast critical R culture form this is the main response when the peritoneal route of inoculation is employed. It thus becomes distinctly possible that there exist certain by-products—pathologically speaking—of the tuberculous process in which this relatively nonacid-fast progeny may be the sole organism isolated and in which the tissue response may be too nonspecific to make the diagnosis from it alone. Yet from a close study of the clinical background of the patient one may get much more definite evidence of the existence of tubercle.

In fact, we have observed several cases supporting this point of view in which the clinical manifestations were not of the type we report here; we mention the fact merely because it harmonizes with our general conception of the rôle of this dissociation cycle of the tubercle bacillus and its possible bearing on the pathologic and the clinical manifestations of this protean disease. This aspect of the subject is being studied further, and the results of these studies will be reported in another communication if occasion seems to warrant.

### A SPECIAL TUBERCULIN FOR THE CRITICAL ROUGH FORM

It is noteworthy that the tuberculin produced by this new organism is not identical with the specific tuberculins of the known tubercle types. Guinea-pigs sensitized with the killed virulent S cultures react to intradermally introduced S tuberculin and partially to critical R tuberculin. But guinea-pigs sensitized by killed cultures of the critical R form, although reacting strongly to the homologous tuberculin, react scarcely at all to Koch's tuberculin!

Moreover, tuberculin made from a critical R avian strain is not distinguishable from that derived from a critical human line—an indication, it would seem, of loss of type specificity paralleling in a general way the loss of species specificity as manifested by the tissue responses.

The finding of a tuberculin with the aforementioned characteristics suggests at once that the apparent anergy observed in the respective cases may have its explanation in the type of tuberculin employed. The results in a few cases of noncaseating epithelioid tuberculosis in which tests were made afford some support for the suggestion, although the work has not progressed far enough to permit one to draw conclusions.

So far as we have gone, these specific reactions are in line with those noted by Beaven [6] who in a large series of cases frequently found that patients reacted to the filtrate from his strain but not to the conventional tuberculins. Although he and Bayne-Jones [7] have not satisfied themselves as yet that this organism belongs in the tubercle bacillus group, our study of it shows that it has so much in common with our critical R variant that we shall not be surprised if eventually it finds definite allocation in this group.

## COMMENT

Anomalous forms of tuberculosis such as the type with which we deal here have in the past been explained either as some other type of infection or, their tuberculous origin granted, largely on the basis of host factors, the nature of which have been entirely obscure. While it is not our intention to dismiss those agents as probable factors, it now seems likely that as the result of the interaction between the host and the parasite new dissociants of the latter may occur that seem more directly responsible for the pathogenesis than has been clear on the basis of the recognition that the Koch bacillus existed in but a single phase.

With recognition of the polyphasic character of the organism, there may be a certain reconciliation between the original contrasting views of Koch and Virchow. The latter was never able to bring himself to believe that a single microbic entity could be responsible for the protean pathologic manifestations of tuberculosis, although Koch's experimental demonstration was overwhelming at the time. It may be that the interplay between host and parasite results in the evolution of phases of the parasite that modify considerably the clinical course and pathologic manifestations of the disease.

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6. Beaven, Paul: Personal communication to the authors.

7. Beaven, Paul, and Bayne-Jones, S.: Mycobacterium (Ryan Strain) Isolated from Pleural Exudate, J. Infect. Dis. **49**:399, 1931.

The inclusion on experimental grounds of an actinomyces-like stage in the life history of the tubercle bacillus is a vindication of the position taken by Metschnikoff,[8] Coppen-Jones [9] and other earlier observers who suspected on morphologic evidence alone that such a stage might exist. The proof of course rested on the actual dissociation of such forms which have been previously reported by Karwacki,[10] Møllgaard [11] and others. But again their evidence lacked completeness until such forms were reverted to an acid-fast bacillus with a demonstrated connection with Koch's bacillus. The reversion in the case reported here fills this last gap in the evidence.

By proceeding along the same lines as were employed in this study, one of us (Dr. Mellon) cleared up a similar paradox in regard to the mycology of blastomycosis. A yeast type and a mold type of the parasite [12] were well known to have been isolated in different cases. But on the theory that both types were phases of a single organism each type was isolated from lesions of different age in the same patient, and later they were dissociated in vitro. Thus it is seen that the polyphasism of the fungi and that of the bacteria are not essentially different with respect to the type of dissociational change under discussion, and that certain manifestations of parasitism may be clarified by keeping these facts in mind.

## KAHN'S "CYCLE" FOR THE TUBERCLE BACILLUS

It is important that the reader does not confuse our dissociation cycle with the one described by Kahn [13] for the tubercle bacillus. His work may be summed up as follows: The tubercle bacillus may under certain conditions become nonacid-fast and in that phase segment into smaller forms and "granules," which again revert to the original acid-

8. Metschnikoff, E.: Ueber die phagocytäre Rolle der Tuberkelxiessenzellen, Virchows arch. f. path. Anat. **113**:63, 1888.

9. Coppen-Jones, A.: On the Morphology and Classification of the Tubercle Fungi-Form and Club-Form in Actinomycosis and Tuberculosis, Centralbl. f. Bakt. (Abt. 1) **17**:70, 1895.

10. Karwacki, L.: Morphology of the Streptothrix Revealed by the Transformation of the Tubercle Bacillus, Compt. rend. Soc. de biol. **100**:214 (Jan. 25) 1929.

11. Møllgaard, H.: Variation and Life Cycles, Beitr. z. Klin. d. Tuberk. **77**: 83, 1931.

12. Mellon, R. R.: Studies in Microbic Heredity: VI. The Infective and Taxonomic Significance of a Newly Described Ascospore Stage for the Fungi of Blastomycosis, J. Bact. **11**:229, 1926; Studies in Microbic Heredity: VII. The Genetic Origin of the Several Types of Fungi Found in the Lesions of Blastomycosis Hominis, ibid. **11**:419, 1926.

13. Kahn, M. C.: A Developmental Cycle of the Tubercle Bacillus as Revealed by Single-Cell Studies, Am. Rev. Tuberc. **20**:150, 1929.

fast bacillus. In other words, the so-called cycle involves merely a change in form, size and staining properties, and there are no dissociative variation, no indication of stabilized culture phases and no functional change of any sort.

Indeed, Kahn [14] would segregate his observations from any type of dissociation involving stabilization of the nonacid-fast forms; he has repeatedly taken the position that the latter are air-borne contaminants. Nor could he find any indication that his "granules" were filtrable. In thus isolating his observations both from the cytologic and from the cultural background of modern dissociational theory and practice, he negates what biologic significance might otherwise attach to them. For in our experience it has been demonstrated over and over again that this pleomorphic cycle of Kahn's, recapitulating as it does a nonacid-fast phase, forecasts by the same token a latent potentiality for the cultural dissociation of this phase as a stabilized (albeit reversible) variant. This is the very evidence which, when it occurs, Kahn casts aside as indicative of contamination.

And in so doing Kahn seems not to have grasped the significance of other evidence,[1a, b] even more critical, which in our opinion makes his whole position untenable. That is to say, the very dissociants which he calls "contaminants" have been reverted to the critical R form of the tubercle bacillus which we have discussed. Could any one sensibly desire more categorical evidence that the nonacid-fast dissociants are not contaminants?

And this capability for reversion applies not only to our original nonacid-fast strains (which were obtained from filtrates) but to a strain originally dissociated by Miller [1d] from the classic H-37 human strain. Kahn's studies of the Miller strain led him to the same conclusion as that to which he came with reference to ours, namely, that it was a contaminant. It is therefore pertinent for us to state that we have also observed the spontaneous reversion of the Miller strain to our critical R acid-fast strain, which is indistinguishable from those dissociated from the virulent S forms.

Moreover, this has taken place in a single cell culture. This precaution was deemed necessary by virtue of the fact that the Miller strain was never free from a few acid-fast forms; to say nothing of our desire to forestall the ever ready contamination criticism, which continues to be employed while the relevant data of published experiments ruling it out are ignored.[1a, b]

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14. Kahn, M. C., and Nonidez, José F.: The Rôle of Non-Acid-Fast Rods and Granules in the Developmental Cycle of the Tubercle Bacillus, Am. Rev. Tuberc. **34**:361, 1936.

Had Kahn viewed his own observations as a recapitulation phenomenon, he would not so easily have been led into the error of interpreting the Miller nonacid-fast strain as a contaminant. For the few acid-fast forms that even single-celled cultures of it contained represented in a sense merely the reverse side of his own experiment. In other words, the recapitulation of the acid-fast forms in a nonacid-fast strain forecasts the possibility of their actual dissociation—and as our experience has it, by a rather definite cytologic mechanism.[15]

That is to say, major dissociations of this sort have previously taken origin directly from rather large sporelike coccoidal forms. Usually they are not observed in the Miller culture, but in the areas of it in which the critical R acid-fast form was being dissociated they were present in such abundance as almost to obscure the bacillary forms. We have in this instance a striking example of how a working hypothesis may predict correctly the dissociative potentialities of a culture. The inadequacy of monomorphic theory in this respect is faithfully represented by Kahn's evaluation of the culture as a contaminant. A valid theory predicts new facts; an outworn one propagates old errors.

Our discussion assumes for the moment the technical correctness of Kahn's cycle as he has described it. But it should be stated nevertheless that workers in general do not agree as to its validity. Kahn has not referred, for example, to the paper of McCarter and Hastings,[16] who were unable to confirm his results when employing his technic. And, although he referred casually to Oerskov's work,[17] he did not point out that Oerskov, using autoclaved cultures in repeating Kahn's technic, observed a type of morphologic change similar to his! Naturally Oerskov's conclusions that his own apparent reversion of the "granules" to bacilli was actually due to crystal formation is not open to question.

Moreover, the thorough attempts of Oerskov to repeat Kahn's results, his long experience and the pertinence of his criticisms of Kahn's technic are such as to demand further proof—which, indeed, Kahn promises will be forthcoming. Others do not consider the demonstration categorical that Kahn's "granules" actually revert to the bacillary form. In such event, their status would not be essentially different from that of the well known Much granules. As a matter

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15. Mellon, R. R.: Studies in Microbic Heredity: V. The Biogenetic Law of Haeckel and the Origin of Heterogeneity Within Pure Lines of Bacteria, J. Bact. **11**:203, 1926.

16. McCarter, J., and Hastings, E. G.: The Morphology of the Mycobacteria, J. Bact. **29**:503, 1935.

17. Oerskov, J.: A Morphological Study of the Initial Growth of the Tubercle Bacillus, Zentralbl. f. Bakt. (Abt. 1) **123**:271, 1931; Further Remarks on the Morphological Studies on the Developmental Cycle of a Single Tubercle Bacillus, ibid. **126**:580, 1932.

of fact, Much expressed the belief that his nonacid-fast gram-positive granules were capable of reverting to the original form of the tubercle bacillus.

In conclusion, our position is that, granting the validity of Kahn's observations, standing alone his "cycle" holds for us no biologic significance, for there has not yet been demonstrated for its nonacid-fast phases anything of functional, biochemical or reproductive significance. One is tempted to think of it as a "cycle of binary fission"! On the other hand, if one attempts to relate it to the biologic background of dissociation phenomena, one may view it as heralding the potentiality for the actual dissociation of nonacid-fast variants, in which event it at least takes on a certain prognostic significance.

Indeed, this would be our present evaluation of it, because in principle its pleomorphic aspects have long been verified not only with the tubercle bacillus but in dissociational studies with other groups of organisms. In a much longer treatise, now being prepared, we may speak of such phenomena as exemplifying a "recapitulation principle"—so often have they become verified in our experience. Yet it is to be noted that this principle does not of necessity require reversion to the "normal form" of pleomorphic structures such as Kahn's.

## CONCLUSIONS

From the early cutaneous lesions of a patient with noncaseating tuberculosis we have recovered in pure culture a partially acid-fast actinomycotic organism.

This has been dissociated into an acid-fast organism which culturally and in other ways is indistinguishable from a dissociant of the virulent S form of the Koch bacillus.

This anomalous variant of the tubercle bacillus, not hitherto described, elicits (under suitable conditions) noncaseating epithelioid lesions in the lungs of guinea-pigs.

It dissociates in vitro and in vivo into the same types of nonacid-fast cultures conventionally recovered from persons with this or with related types of anomalous tuberculosis.

These findings, both factually and pathogenically, are not to be reconciled with the position taken by Kahn, Wycoff and others, who deny to stabilized nonacid-fast forms their status as dissociants of the tubercle bacillus.

NOTE.—Since this paper was written important extensions of the dissociative features of the organisms have been developed. Until a year ago the four year old actinomyces-like culture isolated from the patient grew constantly in the rough colony type so characteristic of the streptotriches. But since that time it has developed several distinct

culture phases, which, however, are generally easily reversible. Literally hundreds of single cells have been isolated in connection with this study.

Although antigenically similar, certain of these phases represent an antigenic unfolding that serves admirably to interlock them with the acid-fast critical R and S strains on one hand and with the nonacid-fast diphtheroids and cocci on the other. This bridging of the antigenic gulf that usually exists between the so-called species and genera may be said to constitute the final step in the integration of these widely separated types into a biologic whole. As such it constitutes a new and useful development in dissociative work.

Moreover, the diphtheroids and cocci mentioned in the text as occurring in other cases have now been dissociated as stable entities from the actinomyces-like culture secured in this case (J. J.). Since they are the other two members of the nonacid-fast biologic triad usually isolated from the lesions in this condition, this fact is of special importance. The dissociation here parallels at several points that thought to obtain in leprosy—a point not only of general interest but specific as well, owing to the fact that some observers have regarded Boeck's sarcoid as a form of leprosy. A full presentation of this work will appear later.

Dr. W. H. Guy, of the Falk Clinic, University of Pittsburgh, referred the patient whose case is reported.

# WHITE PINTA, OR VITILIGO, IN YUCATAN

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In the painstaking census of mal del pinto in Mexico which appeared in 1934,[1] mention was made of the possible existence of an unusual variety of the disease in Yucatan, which was characterized solely by vitiliginous patches. This suggestion apparently originated in a communication of Dr. Rodriguez Arjona [2] to Dr. González Urueña, who conducted the census.

Being interested in pinta as a result of my studies in Mexico and Colombia, I made arrangements with the assistance of Dr. González Urueña to study the question of "white pinta" in Yucatan. In Merida, Mexico, where my observations were made, I became acquainted with the leading physicians of Yucatan and was given every possible assistance by them. I observed numerous cases of the disease in question and learned the views of the Merida physicians on the subject.

As there was no clinic for persons with cutaneous diseases in Merida, patients with "white pinta" were assembled in the offices of various physicians, notably Drs. Palomo Lopez and Magaña Erosa. I obtained the impression that the disease was more common in Merida than in the United States, though this may have been partly due to the fact that the contrast would be unusually apparent in persons of dark complexion (the large majority of members of the population are full-blooded Indians or Indians with an admixture of white blood).

A casual examination of persons with pinta whom I saw on the streets and in the surrounding country districts suggested the presence of either ordinary vitiligo or the terminal stage of pinta, conditions which are identical in appearance. Careful examination in the physicians' offices confirmed the opinions formed by casual observation. The patches were well defined, had convex borders and showed no signs of inflammation or of scratching and no change in the texture of the skin.

It had been claimed by Dr. Rodriguez Arjona that this disease was pinta in which the usual bluish pigmentation was absent. In other words, the disease consisted entirely of vitiligoid depigmentation from the outset. It was agreed by all of the physicians in Yucatan that the patients with this condition never exhibited any of the various shades

1. Primer censo del mal del pinto en la Republica mexicana, 1929-1931, Mexico, Departamento de Salubridad Publica, 1934.

2. Rodriguez Arjona, cited by González Urueña, J.: El mal del pinto, Crón. méd. mex. **30**:126 (March) 1931.

of blue which are so characteristic of pinta. Each patient I examined was asked whether such pigmentation had ever been present, and each invariably gave a negative answer.

The Wassermann test fortunately gives valuable information in the diagnosis of pinta, the percentage of strongly positive reactions being about as high as in secondary syphilis or secondary yaws. Apparently this test had not been used in Yucatan to settle the question of "white pinta." Of the numerous cases which I observed, it was possible to obtain Wassermann tests in only twenty-five. The reaction was negative in twenty-four cases and positive (4 plus) in only one. The patient who had a positive reaction was a man who had a definite history of syphilitic infection twenty years previously and who had received inadequate treatment. Three of the patients who had a negative reaction were said to have had a positive reaction respectively twelve, three and two years previously.

Of the twenty-five patients on whom Wassermann tests were made by Dr. Martinez Palma, thirteen were males and twelve females. Twelve were white persons, five were full-blooded Indians and eight were of mixed Indian and white blood. The ages varied from 7 to 72 years, the average age being 45. The duration of the disease varied from eight months to forty years, the average duration being fifteen and six-tenths years. Of the patients in whom the location was noted, the disease was generalized in eleven and localized in twelve. The commonest location was the backs of the hands (fourteen cases). In one the depigmentation was generalized, and it was possible to be sure of the diagnosis only on the basis of the history of gradual loss of pigment which was given by the patient and corroborated by the family.

In view of the serologic findings and the total lack of bluish pigmentation, the burden of proof would be on one who could consider the disease to be a peculiar type of pinta confined to Yucatan rather than ordinary vitiligo. Dr. Magaña Erosa [3] has expressed in no uncertain terms the view that pinta does not exist in Yucatan, an opinion which was not held by a majority of physicians in Merida.

In discussing the differential diagnosis of pinta and vitiligo I have made no mention of fungi, as in my opinion the weight of evidence is conclusive that fungi play no part in the causation of pinta.

## SUMMARY AND CONCLUSIONS

The claim that there is a type of pinta in Yucatan characterized solely by complete depigmentation is not warranted.

Serologic examination in twenty-five cases of the disease under consideration showed a positive Wassermann reaction in only one case.

The disease in question is apparently ordinary vitiligo.

3. Erosa, Pedro Magaña: Mal del pinto y leucodermias en Yucatan, in Memorias del primer Congresso médico peninsular Yucatan, 1933, p. 70.

# NECROBIOSIS LIPOIDICA DIABETICORUM (URBACH AND OPPENHEIM)

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Descriptions of an apparently new dermatosis intimately associated with diabetes mellitus were first published separately by Oppenheim [1] and Urbach [2] in 1932. Since those original, extensive investigations into the clinical manifestations and histologic picture, several other cases have been presented, and the descriptive name of necrobiosis lipoidica diabeticorum (dermatitis atrophicans lipoidica diabeticorum—Oppenheim) has been generally used in the literature.

In all, I have been able to find fourteen [3] reported cases. Some of these have formed the basis for more or less complete discussion of the condition or some of its phases, while others simply have been presented at various dermatologic meetings. Oppenheim,[1] Urbach,[2] Galewsky,[4] Gottron [5] and Balbi [6] each have reported one case. Two cases each

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From the service of Drs. H. N. Cole and J. R. Driver, Division of Dermatology, City Hospital, Cleveland, and the Department of Dermatology and Syphilology, Western Reserve University, Cleveland.

1. Oppenheim, M.: (*a*) Ueber eine bisher nicht beschriebene, mit eigentümlicher lipoider Degeneration der Elastica und des Bindegewebes einhergehende chronische Dermatose bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica), Arch. f. Dermat. u. Syph. **166**:576, 1932; (*b*) Eigentümliche disseminierte Degeneration des Bindegewebes der Haut bei einem Diabetiker, Zentralbl. f. Haut- u. Geschlechtskr. **32**:179, 1929; (*c*) Eigentümliche Bindesgewebsdegeneration, ibid. **36**:162, 1931; (*d*) Eine noch nicht beschriebene Hauterkrankung bei Diabetes mellitus (Dermatitis atrophicans lipoides diabetica), Wien. klin. Wchnschr. **45**:314 (March 4) 1932.

2. Urbach, E.: (*a*) Eine neue diabetische Stoffwechseldermatose: Nekrobiosis lipoidica diabeticorum, Arch. f. Dermat. u. Syph. **166**:273, 1932; (*b*) Necrobiosis lipoidica diabeticorum, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2, p. 352; (*c*) Kutane Lipoidosen, Dermat. Ztschr. **66**:371 (June) 1933.

3. Since submission of this paper for publication six additional cases have been reported, one each by Usher and Rabinowitch (Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **35**:180 [Jan.] 1937) and Bernstein (Necrobiosis Lipoidica Diabeticorum [Urbach]: Comparison with Granuloma Annulare, ibid. **36**:282 [Aug.] 1937) and four by Michelson and Laymon (Necrobiosis Lipoidica Diabeticorum, ibid. **35**:1130 [June] 1937).

4. Galewsky, E.: Necrobiosis lipoidica diabetikorum (Urbach), Zentralbl. f. Haut- u. Geschlechtskr. **43**:252, 1933.

*(Footnotes continued on next page)*

have been discussed in papers by Zeisler and Caro [7] and Michelson and Laymon.[8a] The remaining five cases were presented at meetings and have not yet been reported in full. Of these, Kren, Klaber and Urbach have shown one each, and Michelson and Laymon [8b] have presented two more. The papers by Oppenheim,[1a] Urbach,[2] Balbi,[6] Zeisler and Caro [7] and Michelson and Laymon [8a] covered the pathogenesis, histology and histochemistry of this condition thoroughly.

## REPORT OF A CASE

*History.*—E. G., a Jewess aged 34, has been followed irregularly in the Cleveland City Hospital and Dispensary since 1930. She first applied for treatment for obesity and menstrual irregularity, and at that time diagnoses of cystocele, rectocele, thyro-ovarian hypofunction and diabetes mellitus were made. Her reaction for urinary sugar was 4 plus, and the sugar content of the blood was 195 mg. per hundred cubic centimeters. On a restricted diet she lost some weight, and the glycosuria disappeared.

In 1931 a diagnosis of chronic tonsillitis with hypertrophic arthritis was made, and also during that year anterior colporrhaphy and perineorrhaphy were done, at which time the urine was still free from sugar and the sugar content of the blood was 141 mg. per hundred cubic centimeters.

During 1932 the patient adhered to her diet poorly, and her weight increased, being recorded once at 250 pounds (113.4 Kg.). In October 1932 a tonsillectomy was performed. It was also during that year that the patient first noticed lesions of the skin. The first appeared on the left breast and gave the patient considerable discomfort because of "an aching pain." No therapy was given, and by May 1933 there were five lesions present, two on the left breast, one on the dorsum of the left hand over the metacarpophalangeal articulation of the first finger and two on the lateral aspect of the right leg—one below and the other just above the knee. At that time a specimen for biopsy was taken, which will be described in conjunction with the report on later ones.

During 1934 and 1935 the patient was seen irregularly, and she admitted almost continuous infractions of her diet. Her reaction for urinary sugar was obtained once and was 4 plus. Three measurements of sugar in the blood showed 266, 228 and 147 mg. per hundred cubic centimeters. Roentgen therapy (320 roentgens) was administered to the lesion on the left hand, but no change followed. In 1935 a series of tuberculin tests were made. With a 1:10,000 dilution the reaction was 3 plus, while greater dilutions gave negative results.

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5. Gottron, H.: Dermatitis atrophicans lipoides diabetika, Zentralbl. f. Haut- u. Geschlechtskr. **42**:721, 1932.

6. Balbi, D. E.: Ricerche intorno alla patogenesi della necrobiosis lipoidica diabeticorum Urbach-Oppenheim, Gior. ital. di dermat. e sif. **74**:14 (Feb.) 1933.

7. Zeisler, E. P., and Caro, M. R.: Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **30**:796 (Dec.) 1934.

8. Michelson, H. E., and Laymon, C. W.: (*a*) Necrobiosis Lipoidica Diabeticorum (Urbach): Dermatitis Atrophicans Lipoides Diabetica (Oppenheim), J. A. M. A. **103**:163 (July 21) 1934; (*b*) Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. **33**:900 (May) 1936.

In that period a new lesion developed on the right forearm, and the old ones increased slightly in size. A few months later the patient complained of severe pruritus vulvae and a cutaneous eruption under the breasts, for which she was admitted to the hospital on Nov. 11, 1935.

*Physical Examination.*—The patient was obese (220 pounds [99.8 Kg.]), mentally alert and not acutely ill. The eyes, ears, nose and throat were normal. Many teeth were absent, and several were carious. A small soft subcutaneous tumor was noted in the left supraclavicular area, which appeared to be a lipoma. The heart appeared normal under percussion and auscultation. The blood pressure was 148 systolic and 98 diastolic. The breasts, abdomen and extremities were normal. A slight white vaginal discharge was noted, and several small hemorrhoidal tags appeared at the rectum. The skin in general was soft and of normal coloration. Beneath the breasts, which were pendulous, was an excoriated papular

Fig. 1.—General view, showing distribution and configuration of lesions on the right leg. There is no ulceration.

erythematous eruption (infectious eczematoid dermatitis). To the right of and slightly above the symphysis pubis was a small furuncle. Surrounding the vulva and perianal region was an area of moderate hyperpigmentation, exhibiting many linear excoriations.

Two circular cutaneous lesions appeared on the left breast and one on the dorsum of the left hand over the metacarpophalangeal articulation. Each of these measured about 3 cm. in diameter, and they were dense cutaneous infiltrations, well circumscribed and of a violaceous, coppery color but without xanthomatous or telangiectatic changes. On the right leg were scattered seven lesions (fig. 1), on the left leg five and on the right arm two. These were apparently of identical character, varied from 7 mm. to 4 cm. in diameter, and were in different stages of development. All were asymptomatic except the largest, on the right calf (fig. 2), which was slightly painful on pressure. All the lesions

were very slightly raised but well defined and definitely infiltrated. In each a violaceous and brownish red border, several millimeters wide, gradually merged with the larger, central portion, which was markedly xanthochromic, spotted with miliary dull red areas and traversed with a lacy, well marked telangiectasia. The larger macules had a definite shine when viewed tangentially and appeared as if they had been painted with collodion or "covered with a tightly stretched layer of cellophane."

*Laboratory Findings.*—The red cell count and the hemoglobin content of the blood were normal. The white cell count was 10,400, and the differential count showed 75 per cent neutrophils, 15 per cent lymphocytes, 9 per cent monocytes, 1 per cent basophils and no eosinophils. Examination for Trichomonas vaginalis

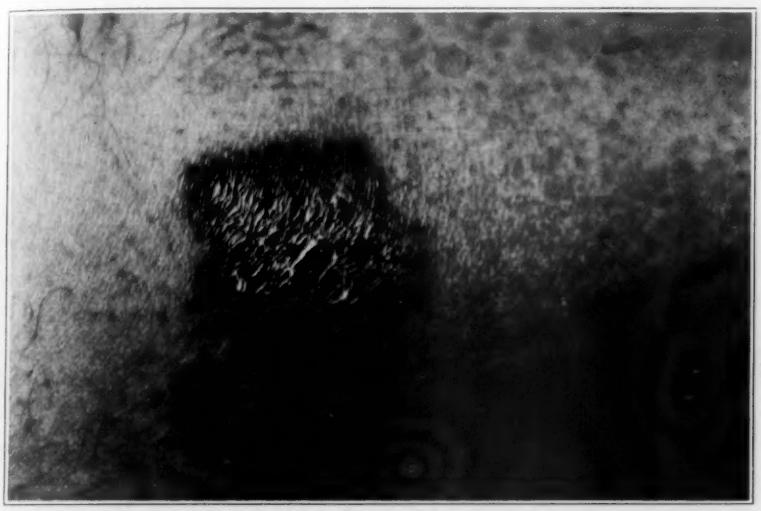

Fig. 2.—Close-up of the large lesions just below the knee. The telangiectasia does not show.

gave negative results. Urinalysis gave negative results except for a 4 plus reaction for sugar. Variations in the patient's condition are tabulated as follows:

| Date | Blood Sugar, Mg. per 100 Cc. | Cholesterol, Mg. per 100 Cc. | Urinary Sugar |
|---|---|---|---|
| 11/13/35 | 279 | 195 | ++++ |
| 11/18/35 Insulin therapy begun | | | |
| 11/19/35 | 169 | 142 | ± |
| 11/26/35 | 149 | ... | Negative |
| 12/ 5/35 | 118 | 177 | Negative |
| 12/18/35 | 124 | 153 | Negative |
| 12/30/35 | 116 | 168 | Negative |
| 5/28/36 | 287 | 260 | ++++ |

On May 28, 1936, after a lapse in insulin therapy and dietary control, studies of the blood lipoids were made. These showed total fatty acids, 550 mg.; neutral fat, 340 mg.; phosphatide, 625 mg., and cholesterol, 260 mg., per hundred cubic centimeters of blood plasma. At this time a specimen of the blood showed a sugar content of 279 mg. per hundred cubic centimeters.

*Biopsy* (description by Dr. E. B. Helwig).—Histologic examination of specimens of skin taken from three different lesions on three different occasions over a period of three years disclosed essentially similar pictures (fig. 3). The epithelium showed occasional mild hyperkeratosis, slight intercellular edema and a varying degree of flattening of the rete pegs. No exudative cells were observed in the epithelium, and the basal cell layer was intact and without increase of pigmentation.

The blood vessels of the papillary layer were slightly dilated and the quantity of collagen slightly increased immediately beneath the epidermis. The blood vessels throughout the corium, particularly those of the deeper portion, frequently exhibited thickening of the walls, principally due to intimal proliferation. In several instances the thickening was accompanied by complete obliteration of the

Fig. 3.—Section showing relatively anuclear area of necrobiosis on the left, with a giant cell just above and fibroblastic and lymphocytic infiltration below. In the upper right portion is a large blood vessel showing the intimal and adventitial reaction, with marked narrowing of the lumen. In the upper central area is a completely thrombosed smaller vessel. (Hematoxylin-eosin stain; magnification, 150 diameters.)

lumen. Frequently associated with the blood vessels were collections of cells, chiefly lymphocytes, and areas of fibroblastic tissue. However, throughout the corium and at the junction of the corium and the subcutaneous fat were encountered similar collections of cells which were unrelated to demonstrable blood vessels at this plane of section. In addition, one of the biopsies (of the breast) showed numerous giant cells, mostly of the Langhans type, and another (of the thigh) showed a few giant calls of both the foreign body and the Langhans type in the areas of cellular infiltration. Plasma cells were rarely observed, and no polymorphonuclear leukocytes were noted.

Throughout the corium, but somewhat more frequently in the less superficial portions and generally encompassed by the cellular infiltration and some fibroblastic proliferation, were poorly demarcated areas of necrobiosis. The necrobiosis was characterized by anuclear or nearly anuclear areas of acidophilic, thick collagen fibers. In some locations the fibers were highly acidophilic and apparently swollen, whereas in other zones they were granular and indistinct and stained poorly both with eosin and by the Van Gieson method. An elastic tissue stain (Weigert) disclosed an absence of elastic fibers in these areas and their diminution in the intervening tissue. A fat stain (sudan III) revealed many minute pale brownish red droplets within the area of necrobiosis. The sudanophilic droplets appeared larger near the periphery of the lesion and were more numerous along small fibrils (fig. 4). The droplets appeared both without and within cells, but

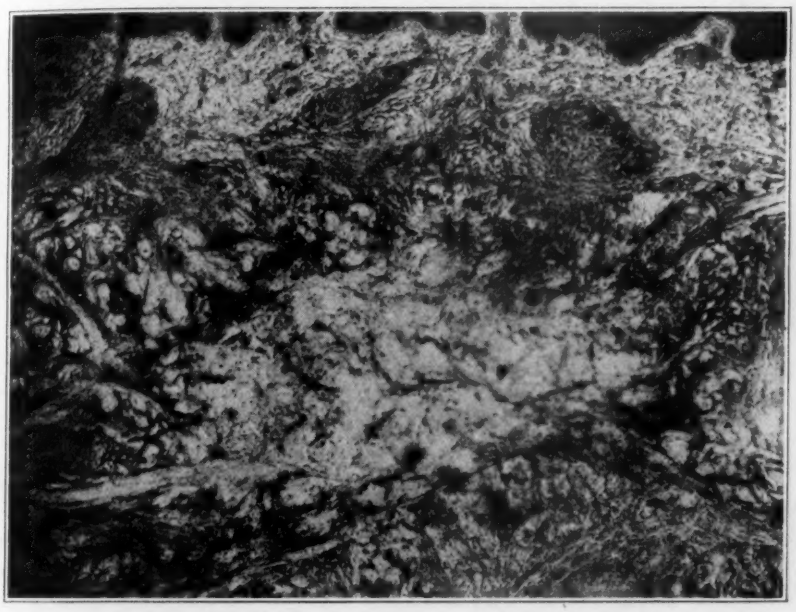

Fig. 4.—Section showing a large necrobiotic focus in the middle portion of the cutis. Extending inward from the periphery of the area are the small fat globules which appear quite dark in the photomicrograph. Surrounding the focus are areas of cellular infiltration. (Sudan III stain for fat; magnification, 150 diameters.)

no sudanophilic histiocytes were noted. The subcutaneous fat stained a brilliant orange red.

*Subsequent Course.*—Shortly after admission the patient was placed on a diet for diabetes, and after insulin therapy the urine became free from sugar (see tabulation). During hospitalization the eczematoid dermatitis, pruritus vulvae and furuncle cleared rapidly. The cutaneous lesions under discussion changed little, if any, despite satisfactory control of the diabetic status, and have continued unchanged since the patient's discharge from the hospital, though she has violated her diet, taken insulin irregularly and shown marked glycosuria on each visit to the dispensary.

*Summary.*—An obese, mildly diabetic woman over a period of several years has had isolated cutaneous lesions clinically typical of necrobiosis lipoidica diabeticorum. Studies of the blood chemistry showed a general elevation of the lipoid elements, while several biopsy specimens exhibited the typical degeneration and infiltrative and vascular changes which have been previously described in this condition. The manifestations in the skin have shown no response to therapy.

## COMMENT

Clinically this case apparently resembles very closely the ones previously described, except those of Balbi [6] and Michelson and Laymon,[8a] in which there were ulcerative lesions. Unfortunately, we were unable to observe the patient when the lesions were in the papular or "first" stage, as described by Oppenheim and Urbach. But the older plaques, with violaceous border, xanthomatous central area and telangiectasia, correspond well with the descriptions in the literature. The oldest lesions (on the left breast and on the hand) have lost their central yellow coloration, are cartilaginous to palpation and possess a violaceous, coppery hue. This, apparently, would fit well with the "third" stage described by Oppenheim, though the central portion has not become white and the lesions have remained clearly demarcated. The distribution of the affected areas in this patient is somewhat unusual, in that there is no great concentration of lesions below the knees, though the lower extremities are more severely involved than other areas.

Owing to the patient's indifferent attitude toward insulin therapy and dietary restriction, I have been unable to test fairly the response of the dermatosis during an adequate period of diabetic control. However, under the routine management of her diabetes in the hospital over a period of several weeks, there was no appreciable change in the lesions. Unfortunately, a diet extremely low in fats, as has been suggested by Urbach, was not given at that time, nor were determinations of the lipoids in the blood made until later.

In a review of cases previously described, it is notable that the appearance of this complication is not dependent on the severity of the diabetes or, more accurately, on the extent of the hyperglycemia. On the contrary, the average value for blood sugar in these cases is 239.4 mg. per hundred cubic centimeters. Several writers have suggested that the condition was, as would be expected, more dependent on the level of lipoids in the blood. Though the reports of cases found in the literature rarely include descriptions of complete studies of the blood lipoids, one is impressed by the high average values in the determinations given. The patient in the case here reported exhibited marked elevation in all the lipoid fractions except cholesterol, which was only moderately increased. The value for neutral fat, 340 mg. per hundred cubic centimeters of blood plasma, and that for total fatty acids, 550 mg., are

considerably above the usual range, while the value for phosphatide, 625 mg., represents a marked increase.

The histologic picture coincides well with those described in the literature. The minimal epithelial involvement, with marked histologic changes in the corium, often situated about pathologic blood vessels and showing severe necrobiosis, cellular infiltration, a diminished quantity of elastic tissue and deposits of lipoid all support the microscopic observations described in the other reports. The fact that some sections show giant cells is at variance with the earlier reports, but recently Kren and Michelson and Laymon [8b] have encountered such pictures.

The interesting hypothesis of Michelson and Laymon,[8a] that this dermatosis is closely allied to diabetic gangrene and is dependent, as Urbach believes, on primary vascular changes, seems tenable in this case. The rather generalized pathologic changes in the blood vessels, often profound and often demonstrably in close association with a necrobiotic focus, make this theory of pathogenesis seem credible indeed.

SUMMARY

A case of diabetes mellitus with typical necrobiosis liopoidica diabeticorum is presented. The histologic picture and the results of chemical studies of the blood are shown to coincide well with those in cases previously described.

# SODIUM AMYTAL AS AN AID TO PSYCHOTHERAPY IN A CASE OF DERMATITIS FACTITIA

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The primary cause of many psychoneuroses is an experience which produces a highly distressing emotional reaction. The mental anguish occasioned by the situation is so great that subconsciously the patient prefers the distraction of simulated physical suffering. The concern over the illness relegates the real issue to the background. Sympathy and attention that are not received when the patient is healthy and escape from unpleasant duties are factors which make this type of illness attractive and preferable. Too often the psychoneurosis is further fixed by a physician's diagnosis of organic disease and the scientific justification of the illness which such an opinion entails.

Unfortunately, the patient is not aware of the connection between his symptoms and their causes. After the physician has gained the complete confidence of the patient, direct, tactful questioning often suffices to bring to light the underlying psychically traumatic situation. The situation itself may not be worthy of the response. Often it is the exaggerated importance the patient attaches to it that wreaks the havoc. Be that as it may, once the physician is cognizant of the primary cause he can direct the patient to an awareness of, and a saner attitude toward, the situation. When this is done, the protective physical symptoms are no longer needed and are readily relinquished, and cure is effected.

In certain cases time does not permit the establishment of the necessary rapport between physician and patient, or else an abnormal amount of resistance is encountered. It is then that the method of breaking down the patient's resistance by the administration of sodium amytal has been found of value.

The indications for, and the technic of, the use of sodium amytal for such a purpose can be illustrated best by the following case, in which the underlying psychically traumatic situation was discovered while the patient was under the influence of sodium amytal and psychotherapy subsequently was successful.

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From the Section on Dermatology and Syphilology, the Mayo Clinic.

REPORT OF CASE

A girl, aged 14, was brought to the Mayo Clinic on Nov. 19, 1935, because of lesions of the skin which refused to yield to treatment. The patient had had good health until October 1934. At that time two lesions had appeared on the midline of the forehead. A physician had been consulted in the course of the first week, and the patient had been under medical supervision more or less constantly since then. The use of ointments, vaccines, arsenical preparations and intramuscular injections of sterile milk had not alleviated the condition. Soon after the lesions had appeared on the forehead, many similar ones had been noted on the arms, legs, thorax and abdomen. For eight months, during the autumn of 1934 and the first part of 1935, the girl had been kept in bed continuously. There had been an improvement in her condition then, but never had the lesions on her face disappeared. For several weeks before the patient's admission to the clinic, the lesions had again become widely disseminated, and she had again been kept in bed.

The family history and the past medical history of the patient were not significant. The physical examination, urinalysis, enumeration of the erythrocytes and leukocytes and differential blood cell count gave negative results, and roentgenograms of the thorax showed no abnormalities. On the face, on the extensor surfaces of both lower extremities and on the flexor surface of the right forearm were many superficial ulcerations. All the lesions had similar characteristics, although they were in different phases of evolution and involution. No primary or elementary lesions were to be found, as the active process was superficial ulceration, usually linear in outline. Crusting, excavations and residual pigmented plaques, the remnants of previous lesions, were found intermingled with the active ulcers. The ulcerations and the pigmentation from the older lesions were noted only at sites which were easily accessible to the patient. There were no lesions on her back, where the patient could not reach. Her mother and sister, who were especially cooperative, said that in repeated observations during the day they had failed to detect the patient in the act of producing the lesions.

A diagnosis of dermatitis factitia was made. Search for the instrument with which the patient produced the lesions was not successful, and when accused of producing the ulcerations with her fingers, she indignantly denied the accusation. Repeated accusations failed to overcome her denial that the lesions were self-induced. Neuropsychiatric study was requested.

The family history gave no indications of nervous diseases. The patient's childhood had apparently been normal. She was described by her mother as having been quiet, serious and ambitious but good natured and sociable. She had been president of her class in school and scholastically had stood third from the top. She professed ambitions to be a nurse, a nun or both.

Since her illness she had been moody, irritable and domineering. She had had one dramatic convulsive seizure which so frightened her parents that a priest had been called. The mother stated that the child had always been extremely modest, and on one occasion when an attempt had been made to discuss menstruation, the patient had responded, "Why do you even want to talk about such things"? The mother and sister said that they had no knowledge of any psychic trauma which the patient might have experienced.

Brief psychiatric examination showed the patient to be overly modest, intelligent, alert, somewhat belligerent and apparently not too dissatisfied with her state. She refused to admit knowledge of any disturbing psychic factors. However, we thought that if the psychic factors in which this personality had been ensnared could be learned and evaluated, cure might be expected. To accomplish this we were faced

with the problem of establishing immediate rapport with an exceedingly disarming patient, as continued care in a hospital was not possible. Accordingly, we decided to try the effect of sodium amytal, administered after the method described by Carns and Washburne.[1] On Nov. 25, 1935, a solution of sodium amytal containing 1 grain (0.065 Gm.) per cubic centimeter was given intravenously at the rate of 1 grain each minute. When 3 grains (0.2 Gm.) had been given, the patient became drowsy, and the injection was discontinued. No excitatory stage was observed.[2]

When the patient gave evidence of inebriation from amytal she was again told that the lesions were produced by herself during sleep. It was explained that her troubled sleep resulted from her subconscious distress over some experience she had undergone and that this experience had greatly worried her and had caused her so much chagrin that she had never discussed it with any one. It was suggested that she could remember the situation by letting her mind dwell on the events prior to her illness. Within a few minutes she recalled a psychically traumatic situation and discussed it freely. It was learned that she had been greatly alarmed by the frequent spells of crying of an older sister. Furthermore, she was perturbed by the intense silence but obvious concern shown by the older members of the family about this sister. She was told nothing and feared to ask questions. When asked if she thought sex might have had something to do with this situation she hesitated and then replied, "I think it did, but I don't know anything about such things, like other girls do."

At this point the examiner consulted the mother and an older sister who accompanied the patient. They were surprised to know that the patient had any knowledge of the matter which had so much concerned them. Then the examiner was told the story of the seduction of the sister whose crying had alarmed the patient. With this knowledge he returned to the patient, and explained to her that another sister, a trained nurse with some experience in psychiatry, who was older and married, was going to tell her the whole story of the episode that had so much troubled her. In addition, she was to be given a much needed educational course concerning sexual matters. She was assured that this knowledge would relieve her of the nervous trouble and that she would again be well and able to return to normal activities and associations. Subsequent correspondence has shown that the program of explanation and education was followed to the letter.

The patient left the hospital the next day. No new lesions appeared after that time, and those present rapidly healed. At the time of writing the patient is attending school, playing in the school orchestra and again associating normally with her classmates. At home she is still irritable and domineering, although less so than previously. At times she resists going to school by complaining of some ache or pain; nevertheless she goes. Her sister believes that at least part of this antagonism results from her disappointment in being a year behind her class. We believe that judicious control of the patient by her family and teachers can effect her complete adjustment.

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1. Carns, Marie L., and Washburne, Annette C.: Psychiatric Investigation in Internal Medicine, Ann. Int. Med. **7**:664-668 (Nov.) 1933.

2. After from 1 to 6 grains (0.065 to 0.39 Gm.) of sodium amytal has been administered by the aforementioned technic, a period of exhilaration, excitement and talkativeness is usually produced. This is the effect desired and indicates that a sufficient amount of the drug has been given. If no excitatory stage is reached, enough is given to make the patient drowsy. W. F. Lorenz (Criminal Confessions Under Narcosis, Wisconsin M. J. **31**:245-250 [April] 1932) recommended that the drug be administered until the corneal reflex is lost.

COMMENT

It has been found by Carns and Washburne,[1] by Lindemann [3] and by Thorner [4] that the proper administration of sodium amytal tends to make normal, psychoneurotic and psychotic persons more accessible and more ready to discuss intimate, emotion-laden subjects concerning which they are otherwise reticent; consequently, psychic investigation can be conducted with a minimal amount of embarrassment when the patient is sufficiently under the influence of the drug. It is claimed, furthermore, that suggestive therapy is received more readily while the patient is in this state. MacLean [5] has suggested that the use of sodium amytal in the manner under consideration may be effective partly because of the enhanced assurance given the examiner. In our opinion, the administration of sodium amytal is a valuable aid when a rapid psychiatric examination of an inaccessible patient is warranted.

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3. Lindemann, Erich: Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **11**:1083-1091 (May) 1932.

4. Thorner, M. W.: The Psycho-Pharmacology of Sodium Amytal, J. Nerv. & Ment. Dis. **81**:161-167 (Feb.) 1935.

5. MacLean, A. R.: Personal communication to the authors.

# TRICHOPHYTIN AND ALLERGY TO TRICHOPHYTIN

## II. OBSERVATIONS ON THE VARIABILITY OF CUTANEOUS RESPONSES TO TRICHOPHYTIN

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In the course of an investigation of the responses elicited in the skin by intracutaneous injections of various trichophyton extracts in a series of over four hundred patients, we encountered an unusual phenomenon in six instances.

Our method of testing the skin of these patients included the injection of 0.1 cc. of each of three different stock trichophytins: (1) a 1:100 dilution of Metz trichophytin prepared from Trichophyton gypseum, Trichophyton cerebriforme, Trichophyton migroides, Trichophyton rosaceum, Trichophyton violaceum and Trichophyton crateriforme—six strains—(2) a 1:30 dilution of Lederle trichophytin prepared from one strain of Trichophyton interdigitale, and (3) undiluted Bischoff dermatomycol, a clasovaccine of Jausion and Sohier prepared from more than three hundred strains of fungi.

When the six patients' skin at the sites of the tests was examined after forty-eight hours, no reactions were visible; but flare-ups were in evidence at one or more of the sites of injection when these areas were observed seven days after the original injections. In other words, in these six patients the cutaneous tests with the trichophyton extracts gave completely negative results when readings were made after forty-eight hours and positive results after the lapse of seven days. This form of flare-up is a well known and common observation in the course of deliberate experimental or spontaneous sensitizations of the skin in both human beings and animals. It was therefore necessary to ascertain whether the reactivity of the skin to trichophyton extracts had been altered in the six persons in whom the sites had flared up after seven days or whether this was simply a peculiar delayed response to trichophytin, constant and characteristic in these six persons.

For this reason we retested the skin of the patients with the same stock preparations of trichophytin, in the same concentrations and in the

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manner previously employed. As can be seen from the accompanying table, all six patients, when retested, reacted definitely to one or more of the stock preparations of trichophytin within forty-eight hours.

This negative response in forty-eight hours to the first intracutaneous administration of trichophyton extracts, followed by a spontaneous flare-up at the site of the test after seven days and followed in turn by a definite response in forty-eight hours to the second intracutaneous administration of the same preparations, embodies the classic characteristics of specific acquired cutaneous sensitization. It is almost identical with what is seen in experimental sensitizations to simple chemicals (i. e.,

*Table Showing Flare-Up Reactions and Results of Retesting with Trichophyton Extracts*

| Patient | Age | Diagnosis | Results of Examination for Fungi | Time Elapsing Between First and Second Injections | Results of the Intracutaneous Injections of Trichophytin | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Lederle (1:30) | | Metz (1:100) | | Dermatomycol (Full Strength) | |
| | | | | | | At 48 Hrs. | At 1 Wk. | At 48 Hrs. | At 1 Wk. | At 48 Hrs. | At 1 Wk. |
| D. W. | 43 | Eczema | Negative | 12 days | 1st injection | 0 | + | 0 | + | 0 | 0 |
| | | | | | 2d injection | ++ | + | ++ | + | 0 | 0 |
| D. R. | 43 | Onychomycosis | Positive | 54 days | 1st injection | 0 | + | 0 | + | 0 | 0 |
| | | | | | 2d injection | + | + | + | + | 0 | 0 |
| B. B. | 44 | Onychia | Negative | 7 days | 1st injection | 0 | + | 0 | + | 0 | 0 |
| | | | | | 2d injection | + | + | + | + | 0 | 0 |
| S. A. | 34 | Eczema | Negative | 47 days | 1st injection | 0 | ++ | 0 | + | 0 | ++ |
| | | | | | 2d injection | + | 0 | ++ | + | ++ | + |
| M. F. | 33 | Dermatitis | Negative | 114 days | 1st injection | 0 | ± | 0 | + | 0 | 0 |
| | | | | | 2d injection | ± | + | + | + | 0 | 0 |
| A. W. | 35 | Verruca plana | Negative | 89 days | 1st injection | 0 | + | 0 | + | 0 | 0 |
| | | | | | 2d injection | + | 0 | 0 | 0 | 0 | 0 |

paraphenylenediamine,[1] neoarsphenamine [2] and butesin picrate [3]) and in sensitizations to foreign serum [4] and plants.[5]

1. Mayer, R. L.: Die Ursolidiosynkrasie des Meerschweinchens, Arch. f. Dermat. u. Syph. **163**:223, 1931.

2. Frei, W.: Untersuchungen mit Neosalvarsan am Menschen, Klin. Wchnschr. **7**:539 (March 18) 1928; Untersuchungen mit Neosalvarsan am Tier, ibid. **7**:1026 (May 27) 1928. Sulzberger, M. B.: Hypersensitiveness to Arsphenamine in Guinea-Pigs: Experiments in Prevention and in Desensitization, Arch. Dermat. & Syph. **20**:669 (Nov.) 1929; Arsphenamine Hypersensitiveness in Guinea-Pigs; Experiments Demonstrating the Rôle of Skin, Both as Originator and as Site of Hypersensitiveness, ibid. **22**:839 (Nov.) 1930.

3. Sulzberger, M. B., and Wise, F.: Drug Eruptions: Dermatitis Eczematosa Due to Drugs, Arch. Dermat. & Syph. **28**:461 (Oct.) 1933.

4. von Pirquet, C., and Schick, B.: Die Serumkrankheiten, Leipzig, F. Deuticke, 1905.

5. Field, H., and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, J. Allergy **7**:139 (Jan.) 1936.

However, it is well known that the deliberate production of experimental sensitization to the extracts of micro-organsims, such as tubercle bacilli and fungi, is extremely difficult, if not impossible; it is generally agreed that the presence of the living micro-organism is usually necessary to bring about a specific alteration in the skin of human beings and animals. For this reason, we must consider the possibility that the specific and the acquired altered response to trichophytin on the part of our six patients were not due to a sensitization de novo, but rather to a specific alteration in a previously existent low degree of sensitivity. In other words, it is possible that our first injections of trichophytin did not create a sensitivity to trichophytin but simply increased an existing nonmanifest sensitivity by speeding up the response, thus intensifying the reaction and shortening the interval between the administration of the allergens and the appearance of the reaction.

A third possible explanation is that these six persons (on five of whom no fungi were observed) nevertheless all harbored fungi (five harboring them in some hidden focus), but that for some unknown reason these fungi alone did not produce a cutaneous sensitivity to trichophytin. However, when we administered our first injections of trychophytin this added allergen plus the action of the living micro-organism sufficed to set in motion the process of specific sensitization of the skin.

No matter what the true explanation may be, it may be stated that the injection of the trichophyton extracts that we employed elicited no response in forty-eight hours but was followed by a flare-up reaction in seven days, and that subsequent injections produced the usual response after forty-eight hours and no flare-up occurred in one week's time at the sites of the second injections.

These manifestations are all undoubtedly to be considered as strong evidence of the production of a specific sensitization, for they embody two of the classic characteristics of the development of sensitivity: (*a*) a reaction to antigen remaining at the site of the first test, which becomes manifest only after a lapse of time necessary to the development of a sufficiently high threshold of cutaneous sensitivity, and (*b*) the speeding of the process of reaction from a reaction appearing in seven days to one appearing in two days. This recalls observations in sensitizations to serum, neoarsphenamine and butesin picrate.[4]

It may not be amiss to call attention to the fact that one of the trichophyton extracts used in our series was the polyvalent clasotrichophytin first developed by Jausion and Sohier [6] and recently recommended

6. Jausion, H., and Sohier, R.: Les claso-vaccins, Presse méd. **37**:621 (May 7) 1930.

by da Fonseca and his collaborators.[7] It is conceivable that this claso-vaccine may have peculiarly active immunologic effects and that this may account for the apparent production of a specific sensitization to trichophytin by means of the injection of trichophyton extracts without the addition of living micro-organisms.

7. da Fonseca, O., Jr., and de Arêa Leão, A. E.: Vaccinotherapia das epidermophyceas e das tinhas tonsurantes, Rev. med.-cir. do Brasil **39**:269 (Aug.) 1931.

# HISTOLOGIC CHARACTERISTICS OF THE SO-CALLED PRECANCEROUS PROCESSES OF THE SKIN

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Much has been done in an attempt to determine the morphologic changes of precancerous degeneration. Some structural changes of the epithelial cells have been pointed out as a characteristic sign of this process; e. g., polymorphism, some cells having several nuclei, has been observed, as well as asymmetrical mitoses and circumscribed cell proliferations. Critical examinations, made by several pathologists, of the changes that have been described did not confirm the supposition that they are of specific significance. According to Bloch,[1] the precancerous process has no morphologic equivalent. Korényi,[2] who in his critical essay examined the significance of each morphologic change observed in these processes, came to the conclusion that the changes hitherto described as characteristic of precancerous degeneration may be present in processes already in the malignant state or in entirely benign conditions. He therefore concluded that they cannot be regarded as the characteristic link between the benign and the malignant epithelial proliferations. The majority of modern authors, regardless of the morphologic structure present, consider as precancerous changes from which sooner or later in a great percentage of instances carcinoma develops. This is of course a purely clinical-statistical definition, but if one ignores the causative factor of the malignant degeneration one is far from able to establish a definition from the patho-anatomic point of view. There is a continuous but slow transition to malignant degeneration, but this transition is morphologically unfixable—*insaisissable,* as Darier designated it. Therefore, so-called precarcinoma cannot be regarded as a state but must be considered as a process (Verebély[3]). From the morphologic point of view the skin is peculiar. It is entirely unknown why there occur in the epidermis cell forms showing an extremely atypical struc-

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1. Bloch, B.: Zum Begriff und Wesen der Praekanzerose, Dermat. Wchnschr. **91**:1164 (Aug. 9) 1930.

2. Korényi, A.: A praecarcinomás stadium birálata kórszövettani vonatkozásban, Orvosi hetil. **78**:801 (Sept. 1) 1934.

ture which in the majority of cases are precursors of cancer. Grütz [4] considered the atypical cells present in Bowen's disease to be the manifestation of the abnormally prolonged stage of beginning of cancer. But it is to be noticed that in the majority of cases cancer of the skin is not preceded by the appearance of such cells. In cases of superficial epithelioma there is no similar degeneration in the environment of the youngest basal cell growth. After commenting on the histologic structure in three cases of Bowen's disease and in three cases of keratosis senilis I shall in the conclusion of this paper answer the following question: Are the aforementioned pathologic changes in the epidermis which have been described as precarcinomatous really precursors of carcinomatous degeneration, that is, do cancer cells develop from these atypical degenerated epithelial cells, or are the changes only coordinated processes in the prickle cell layer caused by the same factor which acts on the basal layer and causes the proliferation of the cylindric basal cells?

## REPORT OF CASES

Case 1.—Sz Gy., a housewife aged 28, had for six months observed a painless erosion on the left labium minus pudendi. On clinical examination there was observed on the superior edge of the left labium minus a nonelevated, moderately infiltrated erosion the size of a lentil, surrounded by a hyperemic zone. I removed the whole efflorescence surgically and cut the excised material longitudinally in two pieces. Histologic examination of the epidermis showed a gradual thickening from the normal part toward the erosion. In the same way, parallel with the formation of acanthosis, the cells of the prickle cell layer had lost their polygonal shape, and the cell boundaries had become less distinguishable, the nuclei of the epithelial cells in this area being oval and light and containing less chromatin. Toward the central parts the polymorphism became more marked: there were several mitoses in the upper layers, cells with two or three nuclei and giant cells with hyperchromatic nuclei. On the edge of the erosion, where no epidermis was to be seen, there were observed in the upper parts of the infiltrated corium round and elongated nests of epithelial cells containing cylindric cells with thin, hyperchromatic nuclei (basal cell heterotopy). The transition from the normal to the acanthotic epithelium with irregular atypical cells was gradual and continuous. The proliferation of the basal cell layer occurred only at the edge of the erosion; in other parts the basal cell layer showed no proliferation.

The diagnosis was Bowen's disease of the vulva with heterotopic proliferation of basal cells in the central parts.

In case 2 the condition was similar.

Case 2.—M. E., a woman aged 47, a cashier, had for a year observed redness and tenderness on the left labium majus pudendi. No ointment employed had

3. Verebély, T.: A praecarcinosis fogalma és gyakorlati jelentösége, Orvosi hetil. **75**:1051, 1931.

4. Grütz, O.: Zur Bowenenschen präkanzerösen Dermatose, Dermat. Wchnschr. **79**:1193 and 1227, 1924.

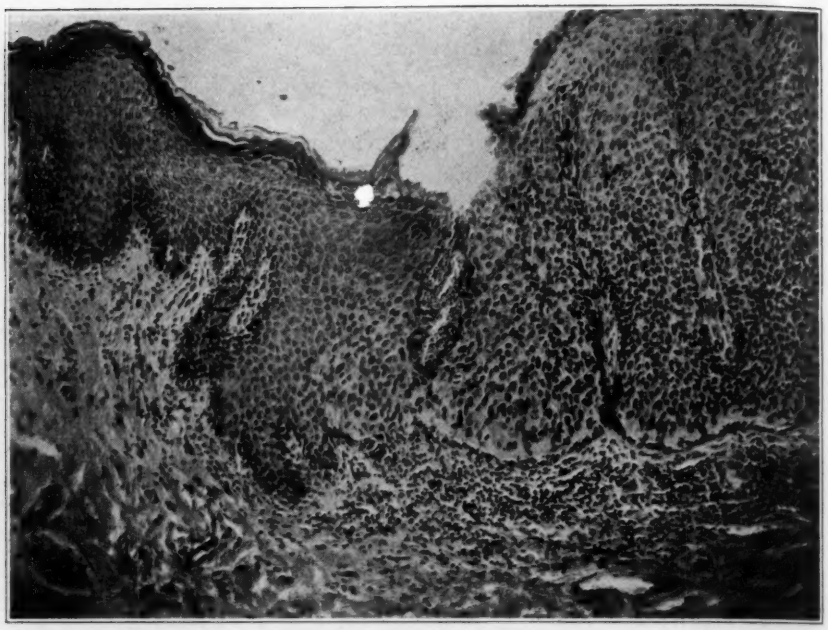

Fig. 1 (case 1).—Gradual thickening of the epiderm from the edges toward the center of the lesion.

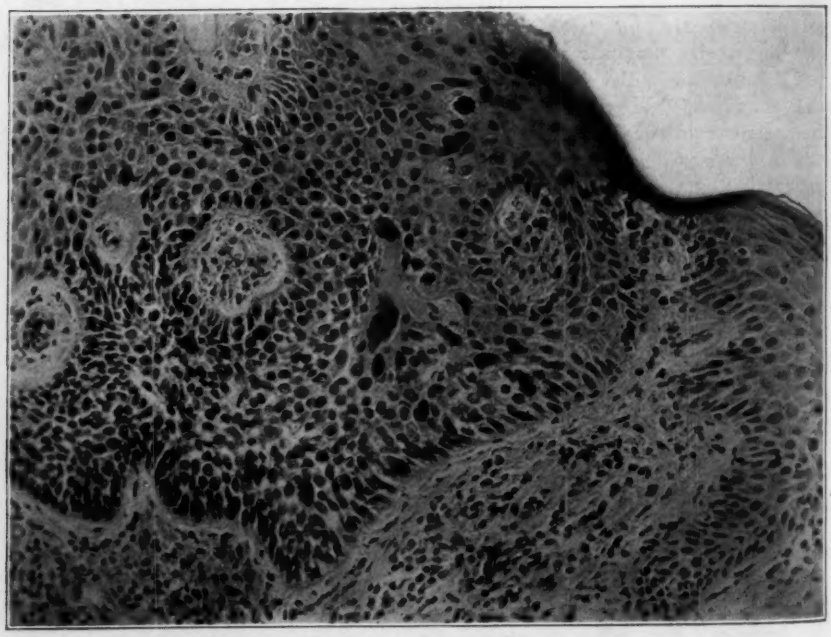

Fig. 2 (case 1).—Typical Bowen cells in the prickle layer.

any effect, and the condition progressed centripetally. Clinical examination showed that on both the left labia the skin was thickened, the surface being hyperkeratotic in some areas and eroded in others. On the labium majus there were slightly papillomatous areas. The hyperkeratotic lesions resembled leukoplakia. Histologic sections of material from the edges and from the central parts of the lesions were made. From the normal areas toward the involved parts the epidermis showed gradual thickening and elongation of the epithelial ledges. This change was accompanied with transformation of the cells of the prickle cell layer. Their polygonal shape and the tonofibrils were lost. The nuclei became larger and ovoid, and their chromatin structure was much looser than normal. The cell boundaries were indistinguishable, and the cells were irregularly placed *Unruhe der Zellen.* Toward the central parts this irregularity was much

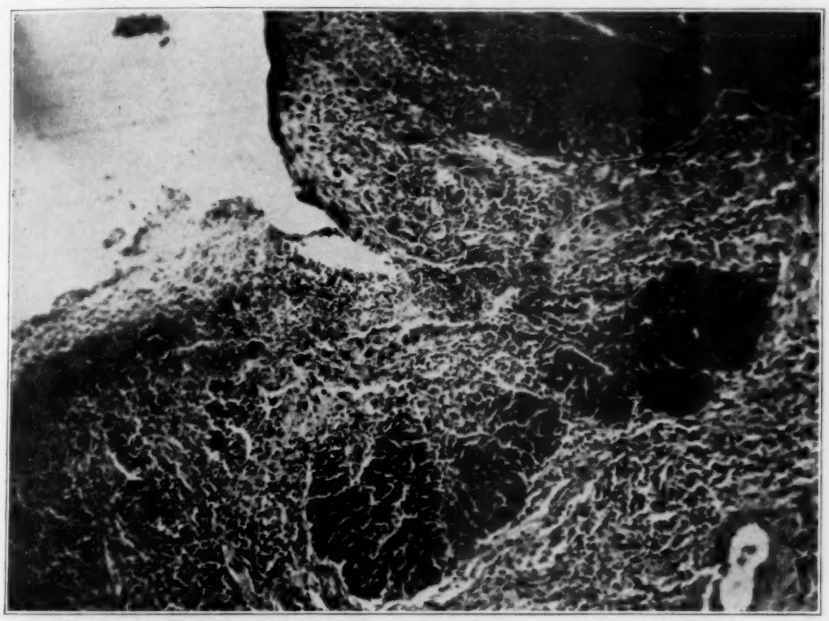

Fig. 3 (case 1).—Basal cell growth in the basis of the central erosion.

more marked; cells with several dark nuclei appeared, and there were scattered cells with monstrous nuclei (clumping cells). In the upper layers of the stratum spinosum many mitotic divisions could be observed. In a section from the inner part of the labium majus a growth composed entirely of basal cells penetrated from an acanthotic epithelial ledge in the depth of the corium.

The diagnosis was gradually developing atypical acanthosis featuring in the inner parts the typical structure of Bowen's disease and in the center a starting basal cell cancer.

Case 3.—K. F., a man aged 52, a polisher, had for a year observed a papillomatous growth on the right buttock. Clinical examination showed on this region a stalked papillomatous growth about the size of a nut, the surface of which was eroded and covered with crusts. The whole growth was excised

Fig. 4 (case 2).—Gradual development of atypical acanthosis of the edge of the lesion.

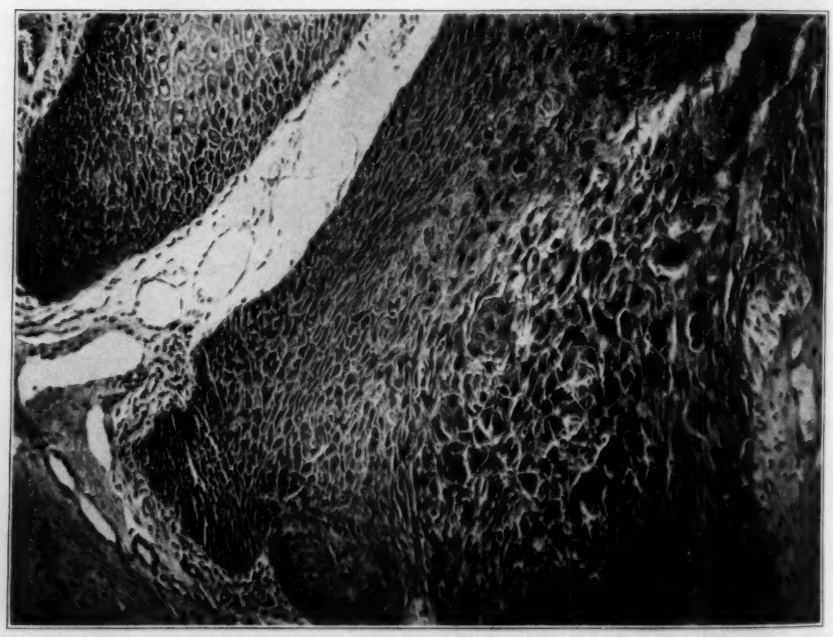

Fig. 5 (case 3).—Beginning anaplasia in an acanthotic epithelial ledge (papilloma).

and examined microscopically. The papilla and the epithelial ledges were enormously lengthened. The epidermis was acanthotic and showed no cellular irregularity except in one prolonged epithelial ledge, where a group of cells could be seen which were irregularly shaped and enlarged and contained hyperchromatic, irregular nuclei. Some of them suggested a similarity with clumping cells (fig. 5). No other parts showed similar cell types, and nowhere could heterotopy or epithelial proliferation be detected.

The diagnosis was papilloma showing in a circumscribed part atypical cells resembling the clumping cells seen in Bowen's disease.

CASE 4.—M. I., a housewife aged 74, had had several dry warts for about six years on the backs of both hands. From one of these lesions on the right hand there developed a horny mass the size of a nut. A month before she presented herself at the outpatient department, she observed a pimple on her upper lip. This grew rapidly and ulcerated. At the clinical examination it was seen to be the size of a dollar and to have elevated edges, and histologic examination of material from the edge of the ulcer showed the structure typical of prickle cell cancer. A histologic examination of material from the horny lesion of the back of the right hand was made too. It showed enormous acanthotic epithelial ledges containing keratotic centers. In some places the epithelial ledges, composed of prickle cells, penetrated in the corium, and so heterotopy could be observed (carcinoma spinocellulare incipiens). I examined histologically material from a dry, nonelevated plaque diagnosed as typical keratosis senilis. The horny layer was thickened and the prickle cell layer reduced to a thickness of 4 or 5 cells. In contrast to the structure of the aforementioned horny lesions, there was no heterotopy, but definitely atypical cells were present: In the atrophic prickle cell layer there were scattered cells with several nuclei and others with monstrous giant nuclei of different sizes and shapes surrounded by normally shaped prickle cells. There was no sign of proliferation toward the corium. In this case there was in two different areas of the skin proliferation of the prickle cells in the corium without appearance of atypical cells (cells with monstrous nuclei and with clumping nuclei); on the other hand, these lesions, which contained no proliferation of the stratum Malpighii even though they showed atrophy, contained many atypical cells as described.

CASE 5.—K. H., a porter aged 69, had for two years observed cutaneous lesions on the temporal regions, on the nose and on the backs of the hands. Yellowish gray flat hyperkeratotic efflorescences the size of a lentil or of a 1 cent piece were present. A histologic examination of material from lesions on the left hand was made. The epidermis showed definite atrophy. In the prickle cell layer, consisting of four or five cell lines, a large number of atypical cells with several or with monstrous nuclei of different sizes could be seen. There were no signs of malignant proliferation.

The diagnosis was keratoma and senile atrophy with atypical intra-epidermal changes.

In case 6 the histologic characteristics were similar.

CASE 6.—D. K., a retired clerk aged 73, for many years had had a wart on the auricle of the right ear. Clinical examination of the lesion showed the typical symptoms of a senile wart. Histologically there could be seen a thickened horny layer but no signs of proliferation toward the corium. In circumscribed places groups of atypical prickle cells could be observed.

The diagnosis was senile keratoma without atrophy and without malignant proliferation but with circumscribed areas showing atypical cells.

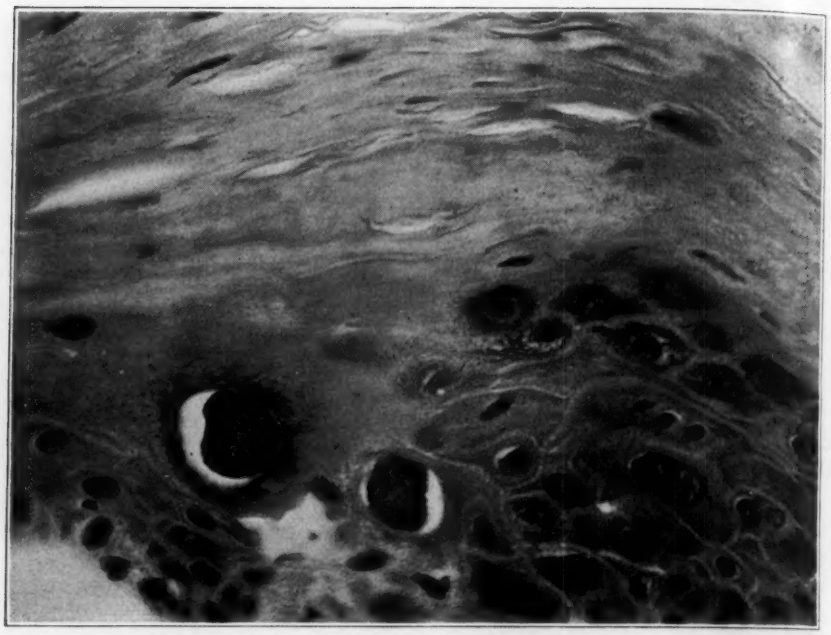

Fig. 6 (case 4).—Giant nuclei surrounded by normally shaped prickle cells (keratosis senilis).

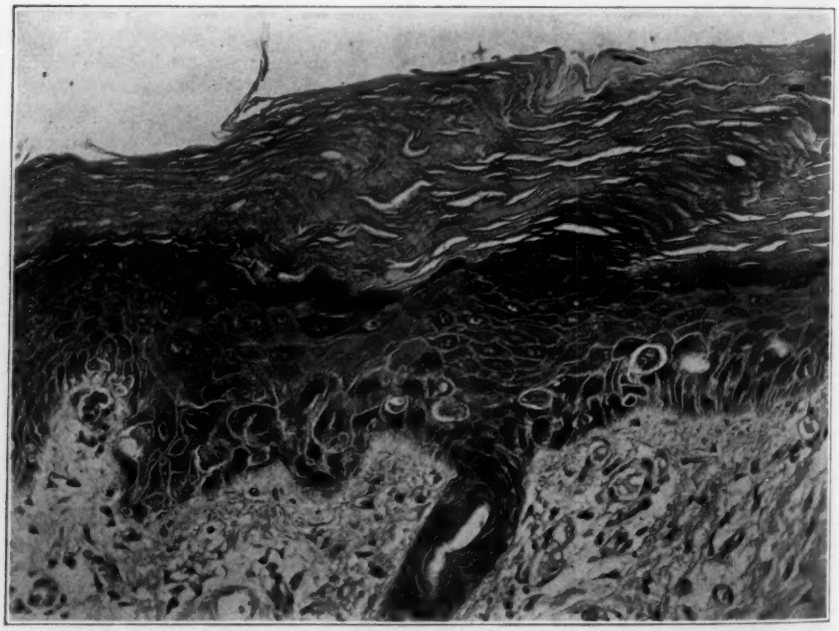

Fig. 7 (case 5).—Anaplastic cells in the atrophic prickle cell layer (keratosis senilis).

## CONCLUSIONS

The histologic examination of material from the boundaries of the lesions described seems to prove that the evolution of the anaplasia (presence of atypical cells) progresses centripetally and that this process is continuous and gradual from the edges toward the center. In the three cases of Bowen's disease I could not observe, even in series of sections, the development of the atypical cells from the ducts of the sweat glands that was described by Pautrier and Grzybowski.[5] Careful examination of the edges of the lesions showed gradual degeneration of the prickle cells. There was no evidence of the intradermal propagation of a fully developed neoplastic tissue originating from one cell or from a circumscribed group of tumor cells. Every cell of the prickle layer seemed to undergo this degeneration.

In cases 1 and 2 the middle parts of this so-called precarcinomatous area—epithelial ledges consisting of cells of basal type—protruded in the depth of the corium. On the basis of the observations that the heterotopic proliferations originating from the lesions of Bowen's disease never contain cells of Bowen type (clumping cells, cells with monstrous nuclei), that they show purely basal prickle cell types and, on the other hand, that there are cases in which the changes of Bowen type remain for a long time localized to the prickle cell layer (typical Bowen's disease, as described by Darier), to the ducts of sweat glands (Pautrier [5]) and rarely to the sebaceous glands (Rousset) it seems probable that the same causative factor brings about degenerative changes in the prickle cell layer and heterotopic proliferation of the basal cell layer. In the majority of cases the latter change occurs (typical basal cell cancer); rarely only the prickle cell layer is affected by this unknown factor, and more rarely both processes develop simultaneously in the same area. I need not mention that as a rule basal cell cancer of the skin begins without any change in the prickle cell layer. I wish to call attention to the multicentric buddings of basal cells observed in superficial epithelioma of the skin which represent the earliest stage of the basal cell proliferation. I know of no one who has succeeded in observing such cell types in areas of such proliferation. According to these observations the intra-epidermal degeneration of the Bowen type seems to be independent of the heterotopic epithelial proliferations, and these cannot be considered as the precursors of cancer; probably they are coordinated changes caused by the same agent. They often occur without heterotopic changes, just as typical cancer develops in the vast majority of cases without the presence of the so-called intra-epidermal precarcinomatous lesions. Morphologically,

5. Pautrier, cited by Grzybowski, M.: L'évolution du cancer de la maladie de Bowen, Ann. de dermat. et syph. **4**:198, 1933.

all the structures and cell forms mentioned as precarcinomatous (cells of Bowen and of Paget type, "intra-epidermal cancer" of Jadassohn, etc.) correspond entirely to the postulates which pathologists proposed for tumors, and therefore they could be considered as intra-epidermal cancers, rightfully named by Broders [6] "carcinoma in situ." Regarding these lesions Broders said:

> It seems pertinent to state that the day has passed when epithelium can be considered noncarcinomatous or at the most only precarcinomatous because it is within the confines of the so-called basement membrane and, conversely, carcinomatous because it has penetrated beyond this barrier.

As I stated in the first part of this paper, precarcinoma is not a state but a process which cannot be determined morphologically.

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6. Broders, A. C.: Carcinoma in Situ Contrasted with Benign Penetrating Epithelium, J. A. M. A. **99**:1670 (Nov. 12) 1932.

# MAPHARSEN IN THE TREATMENT OF SYPHILIS

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The trivalent arsenical preparation meta-aminoparahydroxyphenylarsine oxide was studied originally by Ehrlich and Bertheim and later by Voegtlin and others. Ehrlich and Hata [1] found its therapeutic index to be less than that of the arsphenamines. Voegtlin [2] considered arsenoxide for clinical use in the treatment of syphilis but hesitated because its margin of safety as established by the chemotherapeutic index appeared to be somewhat lower than that of arsphenamine. The attention of chemotherapeutists was again called to arsenoxide as the result of the experiments of Tatum and Cooper.[3] These investigators found that the therapeutic index and other properties were such as to make the drug more promising than any other single antisyphilitic agent. Gruhzit,[4] in studies on experimental trypanosomiasis and syphilis, found that arsenoxide was well tolerated and possessed a therapeutic value at least as high as that of neoarsphenamine.

Mapharsen is meta-aminoparahydroxyphenylarsine oxide hydrochloride, generally known by the generic term arsenoxide. Tatum and Cooper [3a] constructed the name mapharsen—a composition of the first letters in the chemical term. The preparation is a chemically assayable drug of definite constitution, as shown by Tatum and Cooper.[3b] Accord-

From the Departments of Dermatology and Syphilology of the Western Reserve University School of Medicine and of the University Hospital and the City Hospital, Cleveland.

1. Ehrlich, P., and Hata, S.: Experimentelle Chemotherapie der Spirillosen, Berlin, Julius Springer, 1910; cited by Raiziss, G. W., and Severac, M.: Comparative Chemotherapeutic Studies of "Arsenoxide" (3-amino-4-hydroxy-phenylarsenoxide) and Neoarsphenamine, Am. J. Syph. & Neurol. **19**:473 (Oct.) 1935.

2. Voegtlin, C.: The Pharmacology of Arsphenamine (Salvarsan) and Related Arsenicals, Physiol. Rev. **5**:63, 1925; cited by Gruhzit.[4]

3. Tatum, A. L., and Cooper, G. A.: (*a*) Meta-Amino Para-Hydroxy Phenyl Arsine Oxide as an Antisyphilitic Agent, Science **75**:541 (May 20) 1932; (*b*) An Experimental Study of Mapharsen as an Antisyphilitic Agent, J. Pharmacol. & Exper. Therap. **50**:198, 1934.

4. Gruhzit, O. M.: Mapharsen ("Arsenoxide") in the Therapy of Experimental Syphilis and Trypanosomiasis, Arch. Dermat. & Syph. **32**:848 (Dec.) 1935.

ing to Gruhzit,[4] the drug contains 29.01 per cent of metallic arsenic. This arsenical content is approximately the same as that of the arsphenamines, and the effective therapeutic dose is smaller; therefore, the introduction of much less arsenic is required. The drug is an odorless amorphous white powder. It is readily soluble in water. When exposed to air and moisture it is gradually oxidized to a less toxic phenylarsenic acid. In the synthesis of arsphenamine, arsenoxide is the precursive substance and is generally believed to be the first product of the breakdown of the former drug in the tissue. To this fact is ascribed the therapeutic activity of arsphenamine. The solution made up of this drug in the proportion of 4 mg. per cubic centimeter of distilled water is isotonic. The mode of administration is essentially the same as that of neoarsphenamine.

The first clinical investigation of this drug and the first report on its use in the treatment of syphilis in man is that of Foerster and his associates.[5] We obtained a supply of the drug for trial during July 1932.[6] The report of Foerster and his associates [5] dealt with the use of mapharsen alone. Since our investigation has been based on the alternate use of mapharsen and a bismuth preparation and since the report of the Council on Pharmacy and Chemistry of the American Medical Association [7] has stimulated interest in this arsenical preparation, it has seemed wise to present our results.

Our initial experience with mapharsen began on July 23, 1932, and this report includes observations on all patients who received therapy with mapharsen over a period of two years (from July 23, 1932, to July 23, 1934) and data on the therapy and the results of follow-up study of these patients to July 23, 1935. A total of 242 patients received 5,030 intravenous injections of mapharsen, with a total amount of 269,790 mg. Of the 5,030 injections, 1,642, with a total amount of 84,890 mg. of the drug, were given to patients while they were under observation at the hospital; the remainder were given to outpatients. Of the patients with primary syphilis among those studied, 5 had negative and 40 positive serologic reactions. There were 150 cases of early active secondary syphilis, 11 of late secondary syphilis, 34 of tertiary syphilis and 2 of heredosyphilis. The series consisted of 158 males (77 white persons and 81 Negroes) and 84 females (53 white persons and 31

5. Foerster, O. H.; McIntosh, R. L.; Wieder, L. M.; Foerster, H. R., and Cooper, G. A.: Mapharsen in the Treatment of Syphilis, Arch. Dermat. & Syph. **32**:868 (Dec.) 1935.

6. The drug was obtained through Dr. O. H. Foerster and the research department of Parke, Davis & Co.

7. Mapharsen, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **106**:214 (Jan. 18) 1936.

Negroes). The range of ages was from 10 to 69 years; the average age was 28.4 years. The average weight of 222 patients was 124.51 pounds (56.5 Kg.); no weight was recorded for 20 patients. The average period of hospitalization for each patient was twenty-seven and forty-two hundredths days. In this series there were a number of patients who did not continue therapy; some observations on these were available for the record.

All the patients except 3 were hospitalized and were not discharged until free from active lesions, after which they were treated as outpatients. All those hospitalized were subjected to physical examination, a complete blood count and urinalysis. For the patients in the early stages of active syphilis, dark field examinations were made. Wassermann and Kline tests of the blood serum were made; the results were rechecked before the beginning of treatment, and the tests were repeated at varying intervals thereafter and on completion of a course of from 900 to 1,100 mg. of mapharsen and of a course of a bismuth preparation. Spinal puncture was performed before the beginning of treatment in all except 9 cases and when possible was repeated at varying intervals in cases in which positive findings had been obtained. In the earlier period of investigation, examination of the fundi, a phenolsulfonphthalein excretion test and a determination of the urea content of the blood were made as a routine before therapy was begun, in order to establish a base line for possible toxic manifestations. The tests were repeated in a few cases, as deemed necessary. In a few cases the icteric index was determined.

The initial dose injected was 40 mg. or less, 40 mg. being given to 60 patients, 30 mg. to 153 patients and less than 30 mg. to 29 patients. Subsequent doses were 60 mg. or less, 40 or 60 mg. being given in the majority of injections. The largest amount given at a single injection was 60 mg. A course was arbitrarily set as from 900 to 1,100 mg., and these courses were alternated with courses of 10 injections of an insoluble bismuth preparation. Four patients received an initial course of more than 2,000 mg., without apparent harmful effects, the largest amount received continuously in one course being 2,070 mg., given in 35 injections at weekly intervals. Near the end of this period of study, courses of 10 injections, or from 400 to 600 mg., were being instituted.

During hospitalization the first 3 injections were usually given in a period of from ten to twelve days after admission, and subsequent injections were given twice weekly. When observed as outpatients, a few of the first subjects covered by this study received injections twice weekly, but the majority received doses of 40 or 60 mg. at weekly intervals. The preparation of the patient, the mode of administration and the rapidity of injection were the same as those employed in treatment with neoarsphenamine.

This study was made in a large, busy city hospital with a large attendance in the outpatient department. The majority of treatments were given by interns under the direction and supervision of resident physicians.

## DARK FIELD EXAMINATIONS

Dark field examinations were made on material from primary and secondary lesions at varying intervals after the first injection of mapharsen. The result of examination was not considered negative until after two preparations of the deep serum failed to show Spirochaeta pallida.

Among 13 patients with primary lesions who received an initial dose of 40 mg. of mapharsen, 12 showed absence of spirochetes after an average time of nineteen and one-half hours. Four hours was the shortest interval and seventy-two hours the longest. The thirteenth patient received a second injection of 60 mg. forty-eight hours after the initial dose of 40 mg., and dark field examination did not give negative results until seventy-four hours after the initial injection (twenty-eight hours after the second injection).

Of 9 patients with condylomas (affecting the thigh in 2, the vulva in 3 and the perianal region in 4) who received an initial injection of 40 mg., results became negative in 5 in an average time of less than forty-four hours. In the other 4 patients the results of dark field examination were still positive from forty-eight to seventy-two hours after the initial injection. These patients received a second dose, of 60 mg.

For 4 patients with moist erosive papules (affecting, respectively, the prepuce, the thigh, the penis and the scrotum) who received initial injections of 40 mg., negative results of dark field examination were obtained at the end of six and one-third, twelve, three and twenty-three hours, respectively, or in an average of eleven and one-tenth hours.

At the same time that mapharsen was being tried we were also trying thio-arsene (disodium bis [parasulfophenyl] [acetamidophenyl] dithioarsenite) in the treatment of syphilis. Two cases not included in this series are worthy of note. In the first, a patient with a secondary exanthem and perianal condylomas had received 5 injections of thioarsene, with a total amount of 14 cc., over a period of fourteen days, at the end of which time the dark field examination of material from the perianal condylomas still gave positive results. Twenty-four hours after an initial injection of 20 mg. of mapharsen the dark field examination gave negative results. In the second case the patient had received 9 injections of thio-arsene, with a total amount of 43 cc., over a period of twenty-eight days, at the end of which time dark field examination of material from scrotal condylomas still gave positive results. An injection of 30 mg. of mapharsen was given, and dark field examination made seventy-two hours later gave negative results.

The disappearance of spirochetes from lesions under therapy varies with the type and age of the lesion, as well as with the drug used. Since this series of dark field follow-ups is small, and since a busy service prevented routine examination at regular intervals, we feel that too much stress should not be placed on these observations. It appears that in cases of primary lesions a dose of 40 mg. causes the disappearance of spirochetes in less than twenty-four hours in the majority of cases and that in cases of condylomas an initial dose of 40 mg. causes the disappearance of spirochetes in approximately half the cases within forty-eight hours, while in the other half a dose of 40 mg. is insufficient.

### EFFECT ON VISIBLE LESIONS

As regards the healing of primary lesions, we considered the healing of the erosive or ulcerative defect and the disappearance of the syphilitic infiltrate as constituting complete healing, without inclusion of the fibrotic residue of the sclerotic chancre, which may remain for months. Accurate data were available in 19 cases of a primary lesion, in 4 of which there was a negative, and in 15 a positive, serologic reaction.

In the 4 cases of a primary lesion in which the Wassermann reaction of the blood serum was negative, the average time required for the disappearance of the lesion was eleven and seventy-five hundreths days, and the average amount of mapharsen required was 212.5 mg., given in an average of 4 injections—an average of 52.62 mg. for each injection. The shortest time required was eight days; the longest, sixteen. According to the history, the average duration of these lesions prior to therapy was eleven days.

In the 15 cases of a primary lesion in which the Wassermann reaction of the blood serum was positive, the average time required for the disappearance of the lesion was fifteen and thirty-three hundredths days, and the average amount of mapharsen required was 276.84 mg., given in an average of 5.49 injections—an average of 50.42 mg. for each injection. The shortest time required was seven days, and the longest, twenty-nine. According to the history, the average duration of these lesions prior to therapy was twenty and twenty-six hundredths days.

As regards the healing of secondary manifestations, we considered the disappearance of visible eruption and of syphilitic infiltrate as constituting healing, without inclusion of residual pigmentation, which may remain for months. Cutaneous exanthems and mucosal lesions were considered together, and patients presenting large condylomata lata with a visible cutaneous eruption naturally required a longer time for healing than those with a similar exanthem but with no condylomas.

In 80 patients with active secondary manifestations, cutaneous and mucosal, the average time required for the disappearance of the lesions was thirteen and twenty-two hundredths days, and the average amount of mapharsen was 237.87 mg., given in an average of 4.55 injections—an average of 52.28 mg. for each injection. The shortest time required was three days (in a patient with a macular exanthem), the longest forty-two (in a patient presenting large condylomas). The macular and maculopapular lesions healed more rapidly than those of the papular and papulopustular varieties, and the latter healed more rapidly than the grouped follicular ones. The moist, erosive papules of the lips, mouth, axillae, thighs and scrotum healed more rapidly than the large perianal and genital condylomas.

EFFECT ON THE SEROLOGIC REACTION OF THE BLOOD

The Wassermann tests of the blood and the Kline diagnostic and exclusion tests in this series of cases were made by the department of pathology of the City Hospital, Cleveland. The Wassermann tests were made with 0.05 and 0.10 dilutions of serum, cholesterolized antigen being used. The Wassermann and Kline tests were made, and the results were checked in every case before institution of therapy and the tests repeated at varying intervals thereafter and on completion of the course of mapharsen. None of the patients with early syphilis had received previous therapy, and none of the patients with tertiary syphilis had received recent therapy, if any.

TABLE 1.—*Effect of Mapharsen on the Serologic Reaction of the Blood*

| Stage of Syphilis | Number of Patients | Average Number Injections | Average Amount of Mapharsen, Mg. | Average Time of Course, Weeks | Negative Wassermann and Kline Tests | | Negative Wassermann Tests | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Number | Percentage | Number | Percentage |
| **400 to 900 Mg. Course** | | | | | | | | |
| Primary (positive serologic reaction) | 7 | 11.8 | 600.0 | 11.1 | 4 | 57.0 | 6 | 85.7 |
| Secondary, active | 12 | 14.2 | 632.5 | 11.6 | 4 | 33.3 | 6 | 50.0 |
| **900 to 1,100 Mg. Course** | | | | | | | | |
| Primary (negative serologic reaction) | 3 | 17.7 | 1,003.3 | 16.4 | 2 | 66.6 | 3 | 100.0 |
| Primary (positive serologic reaction) | 13 | 18.5 | 1,009.6 | 13.5 | 9 | 69.2 | 12 | 92.3 |
| Secondary, active | 45 | 18.1 | 1,006.4 | 17.0 | 11 | 24.4 | 25 | 55.5 |
| **More Than 1,100 Mg.** | | | | | | | | |
| Primary (negative serologic reaction) | 1 | 27.0 | 1,590.0 | 41.5 | 0 | 0.0 | 1 | 100.0 |
| Primary (positive serologic reaction) | 5 | 26.6 | 1,538.0 | 38.0 | 3 | 60.0 | 3 | 60.0 |
| Secondary, active | 21 | 26.5 | 1,500.2 | 36.0 | 3 | 14.2 | 11 | 52.0 |
| **900 to 1,100 Mg.** | | | | | | | | |
| Tertiary | 12 | 21.0 | 1,048.3 | 18.4 | 1 | 8.3 | 3 | 25.0 |

The summary of results is presented in table 1. The results given were obtained after the initial course of mapharsen and before the use of a bismuth or a mercury preparation.

In the group of patients who received a course of from 900 to 1,100 mg. of mapharsen, of 34 with active secondary syphilis not showing complete reversal of both the Wassermann and the Kline test, examination of the spinal fluid gave positive results in 9. In the group of patients who received a course of more than 1,100 mg. of mapharsen, of 19 with active secondary syphilis not showing complete reversal of both the Wassermann and the Kline tests, examination of the spinal fluid gave positive results in 2. In the group of patients with tertiary syphilis, of 11 not showing complete reversal of the Wassermann and the Kline test, 5 had positive reactions on examination of the spinal fluid. None of the 11 showed any cardiovascular involvement.

Although the number of cases differs from one group to another in table 1, and in the group receiving a course of more than 1,100 mg. the interval of time is longer in proportion to the number of injections received than in the other groups, it would seem that the highest percentage of reversals of the Wassermann reaction in the cases of early active syphilis occurred in the group receiving from 900 to 1,100 mg. of mapharsen. The percentage of reversals for the group receiving from 400 to 900 mg. was almost as high as that for the group receiving from 900 to 1,100 mg.

### EFFECT ON THE SPINAL FLUID

In this series of 242 patients, 233 underwent examination of the spinal fluid before the beginning of therapy. This consisted of a cell count, a Pandy test for globulin, a mastic test and Wassermann tests with 0.1, 0.5 and 1 cc. of fluid. The mastic test and the Wassermann

TABLE 2.—*Results of Examination of the Spinal Fluid*

| Condition | Number of Patients | Number Whose Spinal Fluid Was Examined Prior to Therapy | Number Showing Positive Results | Percentage Showing Positive Results |
|---|---|---|---|---|
| Primary syphilis (negative serologic reaction) | 5 | 5 | 0 | 0 |
| Primary syphilis (positive serologic reaction) | 40 | 36 | 0 | 0 |
| Early active secondary syphilis | 150 | 148 | 21 | 14.1 |
| Late secondary syphilis | 11 | 9 | 1 | 11.1 |
| Tertiary syphilis | 34 | 33 | 8 | 24.2 |
| Heredosyphilis | 2 | 2 | 0 | 0 |

tests were made by the department of pathology of the City Hospital, Cleveland. The results of examination of the spinal fluid are recorded in table 2.

For patients with secondary or tertiary syphilis whose cell counts were above 100 per cubic centimeter, examination of the spinal fluid was repeated one or more times before the patient was discharged to the outpatient department. In those patients whose cell counts were low or the reaction of whose spinal fluid were mildly positive, follow-up punctures were delayed until the end of therapy and after courses of a bismuth preparation, as well as courses of mapharsen, had been administered.

There were 4 patients with active secondary syphilis and 2 with tertiary syphilis whose cell counts were above 100 per cubic centimeter.

In late syphilis of the central nervous system, the cell count of the spinal fluid does not respond so rapidly to mapharsen therapy as it does in early syphilis, and the Wassermann reaction is also slow in its response. The improvement in results of examinations of the spinal fluid under mapharsen therapy is shown in table 3.

TABLE 3.—*Effect of Mapharsen on the Spinal Fluid*

| Data | Before Therapy | | | | | | Preliminary Therapy | No. of Injections | Amount of Mapharsen, Mg. | Course, Weeks | After Therapy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Cells | Pandy Reaction | Mastic Curve | Wassermann Reaction, Amount of Fluid, Cc. 0.1 | 0.5 | 1 | | | | | No. of Cells | Pandy Reaction | Mastic Curve | Wassermann Reaction, Amount of Fluid, Cc. 0.1 | 0.5 | 1 |
| **Secondary Syphilis** | | | | | | | | | | | | | | | | |
| Case 16.—White man aged 28; infection of 4½ mo. duration | 430 | 4 | 3455554321 | 4 | 4 | 4 | Colloidal mercury sulfide, 3 cc. 3 times a day | 5 | 240 | 3.0 | 33 | 4 | 5555432100 | 4 | 4 | 4 |
| Case 39.—Negro aged 25; infection of 5 mo. duration | 600 | 3 | 4554321000 | 0 | 4 | 4 | None | 16 | 900 | 7.4 | 6 | ± | 0000000000 | 0 | 4 | 4 |
| Case 152.—Negro aged 22; infection of 2 mo. duration | 450 | 4 | 5554321000 | 0 | 4 | 4 | Thiobismol, 0.2 Gm. 3 times a day | 11 | 600 | 5.5 | 87 | 4 | 4555554321 | 0 | 1 | 4 |
| Case 167.—White woman aged 34; infection of 6 mo.' duration | 208 | 4 | 4443210000 | 0 | 4 | 4 | Sodium potassium bismuth tartrate, 2 cc. | 13 | 750 | 15.6 | 4 | 1 | 2211000000 | 0 | 0 | 0 |
| **Tertiary Syphilis** | | | | | | | | | | | | | | | | |
| Case 6.—White man aged 31; infection of 7 yr.' duration | 271 | 4 | 5543210000 | 4 | 4 | 4 | None | 18 | 1,020 | 9.3 | 85 | 3 | 5543210000 | 4 | 4 | 4 |
| Case 19.—White woman aged 23; infection of 5 yr. duration | 519 | 4 | 4554321000 | 4 | 4 | 4 | None | 11 | 600 | 5.1 | 16 | 3 | 4443210000 | 4 | 4 | 4 |

In those cases of active secondary syphilis in which there is a high cell count in the spinal fluid, it is our custom to give 3 or more injections of a bismuth or a mercury preparation prior to arsenical therapy, in an attempt to avoid a disturbing Herxheimer reaction. In the case of 1 patient, whose cell count was 600 per cubic centimeter, preliminary therapy was omitted in order to observe the effects of mapharsen alone. After an initial injection of 20 mg. a peak temperature of 39 C. (102.2 F.) was reached in nine hours. The patient complained of increased headache; emesis, formerly absent, occurred nine hours and twenty minutes after the injection; otherwise, no alarming symptoms developed. A rather rapid amelioration of symptoms accompanied the improvement in the spinal fluid. This improvement is shown in table 4.

TABLE 4.—*Effect of Mapharsen on the Spinal Fluid in a Case of Syphilitic Meningitis*

| Date | Number of Injections | Amount of Mapharsen, Mg. | Number of Cells | Pandy Reaction | Gum Mastic Curve | Wassermann Reaction, Amount of Fluid, Cc. | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.1 | 0.5 | 1 |
| 10/28/32 | 0 | 0 | 600 | 4 | 4554321000 | 0 | 4 | 4 |
| 11/ 8/32 | 4 | 180 | 215 | 2 | No test made | No test made | | |
| 11/22/32 | 8 | 420 | 32 | 1 | 2210000000 | 4 | 4 | 4 |
| 12/ 6/32 | 12 | 660 | 12 | 1 | 0000000000 | 0 | 4 | 4 |
| 12/20/32 | 17 | 900 | 6 | 0 | 0000000000 | 0 | 4 | 4 |

## MAPHARSEN IN PREGNANCY

In this series there were 11 pregnant patients, in 4 of whom the onset of pregnancy occurred after the institution of mapharsen therapy. In 6 of the 11 cases the drug was well tolerated; in 5 it was poorly tolerated. The end-results in these 11 cases included 2 instances of abortion, one of which was admittedly self-induced, while the other ocurred after a five month lapse in therapy. Neither patient had received more than 6 injections. For 2 patients mapharsen was discontinued because of severe gastro-intestinal reactions. One of these patients tolerated neoarsphenamine well; the other did not. Three patients were lost from observation. The remaining 4 delivered normal infants, 2 of them having had mapharsen therapy before the onset of pregnancy and the other 2 having had it since the sixth and the seventh month, respectively, after the onset of pregnancy. Details of the 4 cases in which normal infants were delivered are summarized in table 5.

## RELAPSE

Of the 185 patients with early active syphilis (primary or secondary) in this series, 44 have not been seen since they were discharged from the wards of the hospital. Of the remaining 141 patients, there were

15 (12 with active secondary syphilis and 3 with primary syphilis and a positive serologic reaction), or 10.63 per cent, who suffered a relapse, mainly as the result of lapse in therapy. The conditions suffered on relapse may be classified as follows as to type: mucocutaneous, 5; cerebrospinal, 4; serologic, 3; cerebrospinal and iritic, 2, and iritic alone, 1. They may be divided as follows as to the time of appearance of the

TABLE 5.—*Effect of Mapharsen in Pregnancy*

| Case | Data | Therapy: No. of Injections | Therapy: Amount | Condition of Baby at Birth | Cord Blood: Wassermann Reaction | Cord Blood: Kline Reaction | Data Obtained on Follow-Up of Baby |
|---|---|---|---|---|---|---|---|
| 20 | Active secondary stage; patient had one year of therapy before onset of pregnancy; Wassermann and Kline tests negative for 1 yr. prior to delivery | 19<br>10<br>19<br>10<br>11 | 1,040 mg. mapharsen<br>bismuth subsalicylate<br>1,120 mg. mapharsen<br>bismuth subsalicylate<br>640 mg. mapharsen | Good | Negative | Negative | Age 9 wk.: results of examination and Wassermann and Kline tests of the blood negative |
| 173 | Primary stage (positive serologic reaction); patient approximately 6 mo. pregnant when therapy was begun | 14 | 770 mg. mapharsen | Good | Negative | Negative | Baby died at age of 4 wk. from pertussis and bronchopneumonia; postmortem observations substantiated clinical diagnosis; no evidence of heredosyphilis |
| 217 | Secondary, asymptomatic stage; patient 7 mo. pregnant when therapy was begun; Wassermann and Kline tests still positive just prior to delivery | 25<br>10 | 1,200 mg. mapharsen<br>sodium iodobismuthite | Good | ++++ | ++++ | Age 1 mo.; results of examination negative; Wassermann tests ++ and +++; Kline tests — and +++; age 19 mo.; results of examination and Wassermann and Kline tests negative; roentgenogram of wrists and ankles normal |
| 252 | Active secondary stage; patient had 3 mo. of therapy before pregnancy; Wassermann and Kline tests negative for 6 mo. prior to delivery | 17<br>10<br>23 | 990 mg. mapharsen<br>bismuth subsalicylate<br>920 mg. mapharsen | Good | No test made | No test made | Age 6 wk.: results of examination and Kline test negative; age 7 mo.; results of examination and Wassermann and Kline tests negative |

relapse after infection occurred: the first six months, 4; the second six months, 7; the third six months, 3, and the fourth six months, 1.

Relapse was not noted in any patient who received therapy regularly at weekly intervals. The lapse of time following the last injection before relapse occurred varied from twenty-five days to eighteen months. The average lapse of time in 12 of the 15 cases was six months; very irregular attendance was responsible in 2 cases, and in 1 case relapse occurred at the end of a course of bismuth therapy.

Of these 15 cases, no bismuth had been given in 8, in which the average number of injections was 11.5; the average amount of mapharsen received was 662.5 mg., and the average lapse of time following the last treatment was five months (there was irregular attendance in 1 case).

Of the 6 patients who had cerebrospinal disease on relapse, 4 had mild but definitely positive reactions on examination of the spinal fluid before the beginning of therapy. With irregular attendance or lapse in therapy, or both, the involvement of the spinal fluid became the prominent feature. The other 2 patients who had cerebrospinal disease on relapse had negative reactions on examination of the spinal fluid before the institution of therapy. Both had active secondary syphilis. One received 22 injections of mapharsen, with a total amount of 1,290 mg., and 5 injections of a bismuth preparation at irregular intervals over a period of sixty-three weeks, at the end of which time examination of the spinal fluid revealed 10 cells, a 2 plus reaction to the Pandy test, a 5554321000 mastic curve and a negative and two 4 plus Wassermann reactions in 0.1, 0.5 and 1 cc. of fluid, respectively. The second patient received 10 injections of mapharsen, with a total amount of 570 mg., over a period of forty days. Following a lapse of twenty-five days after the last injection, the patient appeared with syphilitic iritis, and examination of the spinal fluid revealed 230 cells, a 3 plus reaction to the Pandy test, a 3221100000 mastic curve and one negative and two 4 plus Wassermann reactions. Considering the amount of mapharsen given and the regularity of the injection, the short lapse of time after the last injection and the degree of involvement of the spinal fluid, which was normal prior to therapy, this patient had the worst relapse observed in the series.

Since it is in the nature of syphilitic patients to have a relapse, especially with inadequate therapy and no matter what arsenical is used, it was felt that some data regarding lapse in therapy without evident relapse of the disease would form some basis for comparison and prove an interesting study.

There were 32 patients with active early syphilis (23 with active secondary syphilis and 9 with primary syphilis, of whom 7 had positive, and 2 negative, serologic reactions) whose treatment was allowed to lapse for periods of time ranging from one and one-half to ten months and averaging four and four-tenths months after the last treatment and who did not show signs of relapse after this period.

Of these 32 patients, 25 had received no bismuth preparation. In these 25 the average number of injections was 14.2; the average amount of mapharsen received was 404.4 mg., and the average lapse of time following the last treatment was four and five-tenths months. In 9 of

these 25 patients, all of whom had 4 plus Wassermann and Kline reactions just previous to lapse in therapy, the Wassermann reaction of the blood was negative on their return to the clinic, and 5 of these 9 also had negative reactions to both diagnostic and exclusion Kline tests. Evidently mapharsen itself has a potent action on the course of early syphilis.

### FOLLOW-UP

The time of observation has been too short to evaluate properly the end-results in these cases or to predict the eventual outcome; however, some data are available. In this connection we shall consider briefly only the cases of early active syphilis, the data for which are listed in table 6.

The large number of patients not seen since their discharge from the hospital is due to the fact that they were referred by other clinics

TABLE 6.—*Data Obtained in Follow-Up Study of Cases of Early Active Syphilis*

| Stage | Number of Patients | Number of Deaths | Patients Off Mapharsen Therapy | Patients Not Seen Since Discharge from Hospital | Cases of Subsequent Lapse of Therapy | Patients Observed in Past Year | Patients Still Under Regular Active Therapy |
|---|---|---|---|---|---|---|---|
| Primary (negative serologic reaction) | 5 | 0 | 0 | 1 | 3 | 1 | 0 |
| Primary (positive serologic reaction) | 40 | 1 | 5 | 9 | 18 | 2 | 5 |
| Early active secondary | 150 | 1 | 13 | 34 | 54 | 11 | 37 |
| Total | 195 | 2 | 18* | 44 | 75 | 14 | 42 |

* Because of: toxic reaction, 8; lack of clinical response, 1, and minor reasons not related to tolerance or clinical improvement, 9.

and were referred back to them. The large number whose therapy had been allowed to lapse may be due to the high percentage of transients and wayfarers who attend a city dispensary.

Of the 75 patients with early active syphilis whose therapy had been allowed to lapse, 55 had been subjected to recent serologic study of the blood. Of these 55, 36, or 65.45 per cent, had negative Wassermann reactions, and 23, or 41.84 per cent, had negative reactions to both the Wassermann and the Kline test.

Of the 14 patients with early active syphilis who were observed in the past year, 10, or 71.43 per cent, had negative Wassermann reactions, and 9, or 64.28 per cent, had negative reactions to both the Wassermann and the Kline test. Of the 5 who did not have completely negative Wassermann and Kline reactions, 3 were subjected to examination of the spinal fluid, and positive results were present in 1, whose reactions had been positive before the beginning of therapy and who had been very irregular in attendance.

Of the 42 patients with early active syphilis who were still under therapy on July 23, 1935, 35, or 83.33 per cent, had negative reactions to the Wasermann test, and 24, or 57.14 per cent, had negative reactions to both the Wassermann and the Kline test. Of the 7 patients showing positive Wassermann reactions, examination of the spinal fluid of 3 gave positive results for 2, both of whom had had positive reactions before the beginning of therapy.

Of 21 patients with active secondary syphilis who exhibited positive reactions to examination of the spinal fluid prior to therapy, 9 are still under therapy or observation. Seven of the 9 have had a reexamination from twelve to twenty-four months after the beginning of therapy, and 5 of these 7 had negative reactions. The 2 whose reactions were still positive have had such irregular and insufficient therapy that one could not have expected good results.

### HERXHEIMER REACTION

Observations regarding the Herxheimer reaction were made for two reasons: First, this reaction is generally considered as being due to the rapid destruction of spirochetes. On the basis of this assumption, the degree of reaction would give some indication of the efficiency of mapharsen as a spirocheticide. Second, the Herxheimer reaction may be extremely disconcerting to both the physician and the patient and in cases in which vital organs are involved may cause alarming symptoms for a few hours.

In studying these reactions, an attempt was made to observe not only the focal but the systemic phase as manifested by elevation of the body temperature. The rectal temperature was determined every two hours after each of the first 3 injections. Initial injections consisted of 40 mg. earlier in the period of investigation and 30 mg. later. All second injections were of 60 mg., except in 7 instances, in which they consisted of 40 mg. All third injections were of 60 mg.

Data were available for 102 patients, and our observations are summarized in table 7.

After the initial injection of 30 or 40 mg., it was not uncommon to see the temperature reach 39 C. (102.2 F.) or higher, this elevation being accompanied in many instances by intermittent chills, with little or no elevation following the second and third injections of 60 mg. Of the 102 patients, only 7 showed an elevation above 37.8 C. (100.04 F.) after the second injection, and in none of these was the elevation higher than 38.4 C. (101.1 F.).

Among the patients with primary syphilis whose serologic reactions were positive, the number showing a focal Herxheimer reaction is not listed, since it was difficult to be certain of observations. Often one

could not observe any change in the local lesion, yet the patient would exhibit a marked elevation of temperature.

In the patients with seconary syphilis, exacerbation of the lesions often occurred in from three to six hours after injection, although the intervening period was occasionally longer. In some patients the focal exaggeration preceded the peak temperature; in others it followed this. Thirteen of the 79 patients with secondary syphilis showed a definite focal Herxheimer reaction without an elevation of temperature above 38 C. (100.4 F.).

The focal flare-up and the temperature gradually subsided. In some cases, subsidence had occurred by the patient's bedtime, which was approximately twelve hours after the time of injection. In many cases focal manifestations and an elevation in temperature were still evident at bedtime but were always absent by the next morning.

TABLE 7.—*The Herxheimer Reaction*

| No. of Patients | Stage of Syphilis | Initial Dose, Mg. | No. of Patients with Local Herxheimer Reaction | Temperature, C. | | | No. of Patients with Temperature of 39 C. or Above | Time of Peak Temperature (Hours After Injection) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Lowest | Highest | Average | | Shortest | Longest | Average |
| 10 | Primary (positive serologic reaction)... | 40 | No data | 37.8 | 40.2 | 39.1 | 7 | 1 | 9 | 7.2 |
| 13 | Primary (positive serologic reaction)... | 30 | No data | 37.4 | 40.2 | 38.8 | 7 | 4 | 10 | 7.1 |
| 41 | Secondary, active..... | 40 | 28 | 37.4 | 40.2 | 38.8 | 15 | 1 | 10 | 6.4 |
| 38 | Secondary, active..... | 30 | 30 | 37.0 | 40.6 | 38.0 | 12 | 3 | 12 | 6.6 |

Contrary to the excellent report of Foerster and his associates,[5] these Herxheimer reactions have not been "of such mild and transitory nature as to be negligible." We believe the degree of the Herxheimer reaction to be a reasonably good indication of the potency of the antisyphilitic remedy. It is probably a good thing.

Additional cases of interest, not included in table 7, are those of 30 patients with late tertiary syphilis who received an initial dose of either 20 or 30 mg. of mapharsen. Twelve of the 30 had elevation of temperature to 38 C. (100.4 F.) or higher after the injection. Contrary to the report of Foerster and his associates,[5] Herxheimer reactions were observed in patients with late syphilis. One patient, with a history of infection fifteen years previously and with tertiary syphilids on the skin of the right forearm and the penis, received an initial injection of 30 mg. There was a marked flare-up of the local lesions and a peak temperature of 39 C. (102.2 F.) was reached eleven hours after the injection. After a second injection of 40 mg. the temperature did not rise above 37.8 C. (100.04 F.).

## TOXIC REACTIONS

The toxic effects of arsenical preparations used in the treatment of syphilis are usually classified as immediate and delayed reactions. The immediate reactions comprise mild and severe nitritoid reactions, gastro-intestinal disturbances, abdominal pain, slight cutaneous eruptions, pruritus, headache, weakness or collapse and other less common effects. Delayed toxic reactions include such conditions as exfoliative or crustaceous dermatitis, hepatic and renal effects, neuritis, purpura, hemorrhagic encephalitis and ocular damage.

Regarding mild immediate reactions, we have definite data, positive or negative, on 167 patients of this series of 242 after most of their injections. Of these 167, 93 had minor gastro-intestinal reactions (nausea, emesis or diarrhea, or all three) on two or more occasions. There were definite data, either positive or negative, on the reactions

TABLE 8.—*Immediate Reactions of Mild Degree*

| Type of Reaction | Initial Dose in Hospital (161 Injections) | Subsequent Doses in Hospital (769 Injections) | Subsequent Doses in Dispensary (842 Injections) |
|---|---|---|---|
| Nausea | 17 | 122 | 82 |
| Nausea and emesis | 5 | 91 | 98 |
| Diarrhea | 1 | 35 | 19 |
| Headache | 7 | 11 | 11 |
| Dizziness | 0 | 4 | 5 |
| Malaise | 0 | 2 | 0 |
| Chilliness | 9 | 0 | 1 |
| Chill | 4 | 2 | 1 |
| Salivation | 0 | 3 | 0 |
| Burning of tongue | 0 | 2 | 0 |

to 161 initial injections given in the hospital and on the reactions to 1,611 subsequent injections, 769 of which were given in the hospital and 842 in the outpatient department. These reactions and their frequency are listed in table 8.

If the reactions to the initial injection, which may have been dependent on or related to the systemic phase of a Herxheimer reaction, are disregarded, data on the response to the 1,611 subsequent injections revealed positive reactions following 467, or 28.98 per cent. If one were to assume that the absence of any definite data after each of the remaining injections meant freedom from reaction, the percentage of reactions for the entire number of injections would be 9.75.

There were 8 patients in whom diarrhea, consisting of from 2 to 10 loose watery stools, occurred rather consistently and was an annoying and troublesome feature. This followed doses of 40 mg., as well as doses of 60 mg. Generally this reaction occurred in the hospital, where patients received injections twice weekly. Of the 8 patients, 4 were not seen after discharge from the hospital; the other 4 tolerated weekly injections as outpatients and had only an occasional attack of diarrhea.

It is believed that the biweekly injections were largely responsible for this symptom, as the incidence was much less in patients receiving weekly injections.

There were 15 patients with the more severe immediate reactions. Of these 15, 12 received immediate trial with small doses of either mapharsen or neoarsphenamine after complete subsidence of symptoms or subsequent trial from two to three months later; some had both immediate and subsequent trial. In cases in which immediate trial with one or the other drug was successful, that drug was continued and in all instances was well tolerated. The classification of these reactions and the results of immediate and subsequent trials with mapharsen or neoarsphenamine are given in table 9.

TABLE 9.—*Immediate Reaction of Severe Degree*

| | | Immediate Trial with Mapharsen | | | Subsequent Trial with Mapharsen | | | Immediate Trial with Neoarsphenamine | | | Subsequent Trial with Neoarsphenamine | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Type of Reaction | No. of Patients | No. of Patients | Tolerance | Intolerance | No. of Patients | Tolerance | Intolerance | No. of Patients | Tolerance | Intolerance | No. of Patients | Tolerance | Intolerance |
| Erythema and pruritus | 5 | 2 | 0 | 2 | 3 | 3 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Gastro-intestinal disturbances (severe nausea and emesis) | 4 | 4 | 0 | 4 | 0 | 0 | 0 | 4 | 4 | 0 | 0 | 0 | 0 |
| Chills and fever | 3 | 2 | 0 | 2 | 0 | 0 | 0 | 3 | 1 | 2 | 0 | 0 | 0 |
| Pruritus* | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| Urticaria and patchy erythema* | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 15 | 8 | 0 | 8 | 3 | 3 | 0 | 8 | 6 | 2 | 1 | 1 | 0 |

* No trial with arsenicals.

Among the immediate reactions due to arsenical compounds administered intravenously, the nitritoid reactions or crises always receive prominent mention. The complete absence of nitritoid reactions in cases in which mapharsen therapy was used was reported by Foerster and his associates.[5] We cannot say that we have observed any nitritoid reaction; however, in this series of 5,030 injections there were 4 instances of a vascular crisis or a reaction of some sort which closely resembled the nitritoid reaction. The observations and the notes on the charts in these cases were insufficient to warrant a dogmatic statement.

Regarding the delayed reactions, there have been no instances of encephalitis, neuritis or involvement of the hematopoietic system. There was only 1 case—a case of jaundice—in which it was believed that mapharsen was the only possible factor. This occurred in a 19 year

old white youth after he had received 13 injections, with a total amount of 750 mg., over a period of fourteen and five-sevenths weeks.

There were 4 other reactions (jaundice in 2 cases, acute nephrosis in 1 and dermatitis in 1) for which mapharsen may have been wholly or partially responsible. In 1 case of jaundice the condition was complicated by the presence of malaria; in the other the patient had received 1 injection of neoarsphenamine. An initial injection of 30 mg. of mapharsen was followed four days later by a second injection of 0.45 Gm. of neoarsphenamine, and on the third injection of an arsenical, given five days after the second, 60 mg. of mapharsen was given. Jaundice appeared one week after the third injection, was of moderate degree and disappeared in three weeks. Four months later the patient tolerated a course of 19 injections of mapharsen, with a total amount of 970 mg. The dermatitis in 1 case was probably due to mapharsen. The patient had received an initial course of 15 injections of mapharsen with a total amount of 740 mg., and the last few of these had been followed by nausea and emesis, even with doses of 40 mg. given at weekly intervals. After a course of 10 injections of an insoluble bismuth preparation, given at weekly intervals, the patient received the first injection of the second course of mapharsen, the dose being 20 mg. A moderately severe and protracted dermatitis ensued. The acute nephrosis occurred in a 32 year old white man with active secondary syphilis. Four injections, or the administration of 220 mg. of mapharsen, were followed by a lapse in therapy of six and one-half months. On his return to the clinic the patient received a course of 25 injections of mapharsen, with a total amount of 1,460 mg., at irregular intervals over a period of fifty-two weeks. This course was followed by 6 injections of an insoluble bismuth preparation, given at weekly intervals. Sixteen days after the last injection of the bismuth preparation the patient was admitted to the medical service; he died eight days after admission. Postmortem examination by the department of pathology of the City Hospital, Cleveland, revealed acute nephrosis. The pathologist believed it impossible to define the cause. This case was the only one which terminated fatally. The patient had received both mapharsen and a bismuth preparation, without an apparent reaction. He was a person with chronic alcoholism. That the nephrosis was due to mapharsen is conjectural.

It was felt that further useful information regarding mapharsen could be obtained by giving it a trial in patients who had had reactions from the arsphenamines. Definite data are available on 4 such patients, who were not included in this series. Three of these had a pruritic, erythematous, macular eruption after the second, third and fifth injections, respectively, of neoarsphenamine. After complete subsidence of all the symptoms, an immediate trial with 1 injection of mapharsen in doses

of 15, 20 and 5 mg., respectively, caused recurrence of symptoms. Of these 3 patients, 2 received subsequent trials with similar small doses at intervals of four and one-half and six months, respectively, at which time one again exhibited intolerance and the other tolerated a course of 930 mg. The fourth patient gave a history of severe dermatitis following 3 injections of neoarsphenamine given from five to six years before. A trial with 5 mg. of mapharsen resulted in a severe and protracted dermatitis of an exfoliative character.

### TECHNICAL COMPLICATIONS

Pain in the arm along the course of the vein, frequently extending as high as the shoulder, occurred after 89 injections (13 initial injections and 76 subsequent injections). Since the preparation of this article began, we have had reports that this reaction has been entirely eliminated by rapid intravenous administration of the drug—the opposite procedure to that required with the arsphenamines.

Venous sclerosis has been observed in 6 patients (4 females and 2 elderly males). All these had veins which presented difficulty in intravenous therapy. Five of them have subsequently received from 6 to 11 injections of mapharsen, but with some difficulty.

Extravasation of small amounts of mapharsen or slight perivascular leakage occurred after 18 injections. This was followed by a local inflammatory reaction of slight degree, associated with a burning pain which was, apparently, rather severe. The local reaction and the pain subsided rapidly. Nodular infiltration, formation of abscesses, necrosis and sloughs such as may follow extravasation of neoarsphenamine or arsphenamine were not observed in any case.

### SUMMARY AND CONCLUSIONS

The observations reported here were made in a clinical study of the effect of mapharsen on 242 patients with syphilis, in 185 of whom the disease was in the primary or the active secondary stage. The study extended over a period of three years. The patients received 5,030 injections, with a total of 269,790 mg. of the drug. Therapy consisted of alternate courses of mapharsen and a bismuth preparation.

Observations were made on the disappearance of spirochetes from lesions, the healing of visible lesions, the reversal of the Wassermann reaction of the blood, the effect on the spinal fluid, the effect in pregnancy and the frequency of relapse.

In cases of primary lesions, a dose of 40 mg. was followed by a negative result on dark field examination in less than twenty-four hours in the majority of cases; in cases of condylomata lata, a dose of 40 mg.

was followed by a negative result on dark field examination in approximately half the cases within forty-eight hours, and in approximately half the cases a dose of 40 mg. was insufficient.

For 4 patients with primary syphilis whose serologic reactions were negative the average time required for healing was eleven and seventy-five hundredths days. For 15 patients with primary syphilis whose serologic reactions were positive the average time required for healing was fifteen and thirty-three hundredths days. For 80 patients with active secondary manifestations (cutaneous and mucosal) the average time required for healing was thirteen and twenty-two hundredths days.

The percentage of reversals of the Wassermann reaction of the blood after the initial course of mapharsen (before any bismuth therapy had been given) was greatest for that group receiving a course of from 900 to 1,100 mg. In this group, the percentage of reversals of the Wassermann reaction for 13 patients with primary syphilis and a positive serologic reaction was 92.3, and for 45 patients with active secondary syphilis it was 55.5.

The reduction in the cell count and the globulin content of the spinal fluid under mapharsen therapy was prompt in the cases of early involvement of the central nervous system and less prompt in the cases of late syphilis of the central nervous system.

In this series there were 11 pregnant patients. Two aborted (neither patient had received more than 6 injections); 2 were taken off mapharsen therapy because of severe gastro-intestinal symptoms; 3 were lost from observation, and 4 delivered normal infants at term. Of the 4 infants who were normal at birth, 1 died of pertussis and bronchopneumonia, and postmortem examination revealed no evidence of syphilis. The most recent observations on the remaining 3, made at the ages of 9 weeks, 19 months and 7 months, respectively, were negative clinical and serologic results.

Of 141 patients with early active syphilis who could be followed, there were 15, or 10.63 per cent, who suffered a relapse, mainly as a result of lapse in therapy. Eight of the 15 had received no bismuth preparation. Relapse was not noted in any patient who received therapy regularly at weekly intervals.

There were 32 patients with early active syphilis who allowed therapy to lapse for an average period of four and four-tenths months without showing a relapse. Twenty-five of these 32 had received no bismuth preparation.

A follow-up study of patients with early active syphilis showed 75 who had allowed therapy to lapse. Of these, 55 had been subjected to recent serologic studies of the blood prior to lapse, and 65.45 per cent had negative Wassermann reactions. Of 14 patients with early active

syphilis who were observed in the past year, 71.43 per cent had negative Wassermann reactions. Of 42 patients with early active syphilis who were still under therapy, 83.33 per cent had negative Wassermann reactions. Of 21 patients with active secondary syphilis who exhibited positive reactions on examination of the spinal fluid prior to therapy, 9 are still under therapy or observation; 7 of the 9 have had reexamination, from twelve to twenty-four months after the beginning of therapy, and 5 of these 7 had negative reactions. The 2 whose reactions were still positive have had such irregular and insufficient therapy that one could not have expected good results.

Observations were also made on the Herxheimer reaction, or therapeutic shock, and on toxic manifestations, both immediate and delayed.

The Herxhiemer reaction, in both the focal and the systemic phase, is prominent. With an initial dose of 30 or 40 mg. this reaction was frequently severe. In those cases in which vital organs are affected by syphilis, extreme caution and a conservative initial dose should be employed.

The immediate toxic reactions of a mild degree were chiefly gastro-intestinal disturbances. Of the 167 patients experiencing mild reactions, 93, or 52.69 per cent, had minor gastro-intestinal reactions (nausea, emesis or diarrhea, or all three) on two or more occasions. Data on the response to 1,611 injections revealed mild immediate reactions following 467, or 28.98 per cent. In this series of 242 patients, there were 15 with immediate toxic reactions that were more severe.

Regarding delayed toxic reactions, there were no instances of encephalitis, neuritis or involvement of the hematopoietic system. In 1 case—a case of jaundice—mapharsen appeared to be the only factor. There were 3 other cases, 2 of jaundice and 1 of dermatitis, in which mapharsen may have been wholly or partially responsible. A case of acute nephrosis which followed the injection of mapharsen may have been due to any one of a variety of causes, including chronic alcoholism.

As to technical complications, pain in the arm along the course of the vein occurred after 89 injections. Since the preparation of this article began, we have had reports that this reaction has been eliminated. Extravasation of small amounts of mapharsen or slight perivascular leakage occurred after 18 injections. The local inflammatory reaction and the pain subsided rapidly. Nodular infiltration, formation of abscesses, necrosis and sloughs were not observed in any case.

# SUBSURFACE GROWTH OF PATHOGENIC FUNGI ON PEPTONE, HAIR, PIG SKIN AND CYSTEINE-CYSTINE MEDIUMS

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In a previous paper [1] I made a preliminary report on the predominance of subsurface growth on mediums made with hydrolyzed hair, hydrolyzed pig skin and cysteine hydrochloride. In this paper the types of subsurface growths noted, the variables incident to the correlation of subsurface growth with invasiveness and chronicity of pathogenic fungi for man, and the factors probably accountable for the results are discussed.

Little is known regarding the basic factors accountable for the invasiveness and chronicity of micro-organisms. If anything was to be learned it was evident that if the culture in the test tube was to be studied and correlated, a medium made of tissues for which the organisms were selective was the point of departure. It is known that: 1. The type of growth might yield valuable information. 2. Organisms grown on mediums made of such ingredients as peptone and blood tend to dissociate. This is to be expected since few diseases proved to be caused by micro-organisms are selective for muscle tissues and blood. If organisms in general are dependent on a specific soluble substance for their pathogenicity and for the growth of colonies characteristic of this pathogenicity, the tissues for which they are selective or mediums made therefrom would be expected to best retain this quality. For example, certain pathogenic fungi are selective for hair and skin. It has not as yet been definitely proved that they possess a specific soluble substance responsible for this pathogenicity. The pneumococcus which I shall consider in a later study on pathogenic micro-organisms has been shown to contain a specific soluble substance accountable for its smooth colony and its pathogenicity. In the latter instance, therefore, one would postulate that a medium with lung alveoli, pleura or peritoneum as the basic ingredient would be more apt to retain the aforementioned characteristics.

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Contribution 101 from the Department of Biology and Public Health, Massachusetts Institute of Technology.

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1. Williams, J. W.: Science 83:396 (April 24) 1936.

## SURVEY OF MATERIAL

For simplicity this study is divided into several sections:

*Section I.*—This gives a description from a comparative point of view of growths of pathogenic fungi on mediums designated as follows: (1) S, Sabouraud's proof medium (1 per cent peptone, 4 per cent dextrose, 1.5 per cent agar); (2) Sk, hydrolyzed pig skin medium (1 per cent hydrolyzed pig skin, 4 per cent dextrose, 1.5 per cent agar); (3) H, hydrolyzed hair medium (1 per cent hydrolyzed hair, 4 per cent dextrose, 1.5 per cent agar), and (4) C, cysteine medium (1 per cent cysteine hydrochloride, 4 per cent dextrose, 1.5 per cent agar). The hair and pig skin hydrolysates were made by the Difco Laboratories, Inc., by hydrolysis with dilute sulfuric acid. All the cysteine hydrochloride did not stay in solution, but an even suspension was obtained. Children's hair was chosen, since I felt that slightly better growths were obtained with it than with hydrolyzed hair from adults. When hair from adults was used, however, more brownish pigmentation of growth was obtained. Sabouraud's proof medium was used since on the W medium used as a routine (4 per cent peptone, 1 per cent dextrose, 1.5 per cent agar) the subsurface mycelium was observed with difficulty because of the dark character of the medium. When the 4 per cent hair and 1 per cent dextrose mediums were used in trials, good subsurface growths, somewhat more marked and lending more browning to the mediums, were obtained.

*Section II.*—This gives a description of stab cultures on the following mediums: (1) S, Sabouraud's proof medium; (2) W, W medium (4 per cent peptone, 1 per cent dextrose, 1.5 per cent agar); (3) WH medium (1 per cent hydrolyzed women's hair, 4 per cent dextrose, 1.5 per cent agar).

*Section III.*—In order to rule out the possibility of observations being due to sinking of the growth into the mediums because of lack of compactness of the agar, different concentrations of agar were used, the respective mediums being designated as follows: (1) 0.5 S, Sabouraud's proof medium containing 0.5 per cent agar; (2) 1 S, Sabouraud's proof medium containing 1 per cent agar; (3) 1.5 S, Sabouraud's proof medium containing 1.5 per cent agar; (4) 3 S, Sabouraud's proof medium containing 3 per cent agar; (5) 6 S, Sabouraud's proof medium containing 6 per cent agar.

*Section IV.*—In order to determine the influence of cysteine hydrochloride on growths on Sabouraud's proof medium the following mediums were planted: (1) 0.25 CS medium (0.25 per cent cysteine hydrochloride, 1 per cent peptone, 4 per cent dextrose, 1.5 per cent agar) and (2) 0.25 C medium (0.25 per cent cysteine hydrochloride, 4 per cent dextrose, 1.5 per cent agar).

*Section V.*—In order to determine the effect of cysteine hydrochloride mediums adjusted to different $p_H$ values, the following mediums were employed: (1) cysteine hydrochloride 0.25 per cent, dextrose 4 per cent, agar 1.5 per cent adjusted to $p_H$ 5.6, 6.6 and 7.6; (2) Sabouraud's proof mediums adjusted to $p_H$ 5.6 and 7.6. The $p_H$ of the cysteine mediums after they had been autoclaved was 5.4, 6.1 and 6.6, respectively.

*Organisms Studied.*—The following representative fungi and two nonpathogenic saprophytes, Lichtheimia sp. and Scopulariopsis brevicaulis, were studied: Achorion Schoenleinii, Acladium Castellani, Candida candida, Endodermophyton indicum, Endodermophyton tropicale, Endomyces capsulatus, Endomyces dermatitidis, Epidermophyton crusis, Epidermophyton inguinale, Epidermophyton rubrum, Glenospora Gammeli, Geotrichum Bachmann, Indiella americana, Microsporon Audouini, Microsporon felineum, Microsporon gypseum, Monosporium apiospermum, Monilia albicans, Oospora humi, Sporotrichum Schenckii, Trichophyton balcaneum, Trichophyton crateriforme, Trichophyton decalvans, Trichophyton granulosum, Trichophyton gypseum, Trichophyton gypseum-asteroides, Trichophyton gypseum-lacticolor, Trichophyton interdigitale, Trichophyton japonicum, Trichophyton louisianicum, Trichophyton niveum, Trichophyton purpureum, Trichophyton sulfureum, Willia anomala. All the mediums were adjusted to $p_H$ 5.6. Growths took place in diffused light at room temperature. Descriptions are made of from one to two month growths.

## SECTION I

As noted previously, the following abbreviations are used to designate mediums: (1) S Sabouraud's proof medium; (2) Sk, hydrolyzed pig skin medium; (3) H, hydrolyzed hair medium, and (4) C, cysteine hydrochloride medium.

A cysteine medium was used since this amino-acid varied in the other mediums, peptone medium containing least and hydrolyzed hair medium most. The term cysteine is used since the product purchased was cysteine hydrochloride. However, in mediums used one would expect this reduced substance to be converted in large part into oxidized cystine. This factor is basically important, since cysteine decreases oxygen tension and cystine increases it.

The following data include approximate estimates of salient variations of the colonies on the mediums used. A "growth plate" was noted in many instances. This is defined as a definite line of apparent departure of growth. In some instances it was so definite that it was a crescentric shell-like configuration. Often this plate was sunk into the medium and on its surface could be noted a white mycelial growth

extending toward the surface. Often this subsurface growth was well demarcated peripherally, even though in some instances rootlets of mycelium extended therefrom. Sometimes, as in S, the growth became subsurface peripherally. When the plate was well demarcated it is so designated. In order to denote the amount of growth the designations 1, 2, 3, 4 and 5 plus are used.

*Achorion Schoenleinii.*—On S there was a low irregular cream-colored surface mycelial growth, depressed centrally. There was 2 mm. of subsurface dipping of mycelium peripherally. (Growth, 5 plus.)

On Sk the surface showed a smooth, thin mycelium. The growth plate was 2 mm. below the surface, dipping to 4 mm. peripherally. (Growth, 3 plus.)

On H there was a sparse surface film, especially at the plant. The growth plate was 4 mm. below the surface, dipped slightly at its edge and was rather opaque with slight browning. (Growth, 2 plus.)

On C there was a sparse surface growth. The growth plate was 3 mm. below the surface and rather opaque. (Growth, 2 plus.)

*Acladium Castellani.*—On S the surface growth was well demarcated and extended about 3 mm. below the surface at its edge. The medium was darkened. (Growth, 4 plus.)

On Sk the plate of growth was well demarcated and extended about 1 mm. below the surface. The medium was slightly darker than S. (Growth, 3 plus.)

On H the plate was not well developed. The growth was practically all below the surface and flocculent and had mycelium extending 5 mm. into the medium from the surface. The medium was almost black. (Growth, 2 plus.)

On C the growth was like that on H except that it was not as dark or flocculent. (Growth, 2 plus.)

*Candida Candida.*—On S there was a mortised waxy irregular surface growth gathered up centrally. A growth equally well demarcated extended to 2 mm. below the surface, dipping at its edge. (Growth, 5 plus.)

On Sk there was a waxy surface growth, finely radiate centrally. There was a much greater amount of subsurface growth, extending through the agar below. The growth plate was well demarcated and about 1 mm. below the surface, dipping to 7 mm. peripherally. (Growth, 2 plus.)

On H there was a slight bit of growth at the plant. It extended 6 mm. below the surface and was moderately opaque. There was no definite growth plate. (Growth, 2 plus.)

*Endodermophyton Indicum.*—On S there was a well demarcated irregular radiate powdery surface growth, somewhat translucent and heaped up centrally. The growth extended into the medium 4 mm. at its edge. (Growth, 5 plus.)

On Sk the surface growth was thin, fine, powdery and much flattened, with only slight wrinkling centrally. The growth plate was 3 mm. below the surface, dipping at its edge to 5 mm.; it was opaque and delimited. (Growth, 4 plus.)

On H there was no noticeable surface growth. The subsurface growth was 3 mm. below the surface and showed at its edge crescentic dipping of 1 cm., somewhat translucent, with browning centrally. (Growth, 3 plus.)

On C there was a barely noticeable growth on the surface. The growth plate was 3 mm. below the surface and showed browning centrally; it dipped slightly at the edge. (Growth, 2 plus.)

*Endodermophyton Tropicale.*—On S there was a well demarcated and much wrinkled surface growth with an adherent thin light tan mycelial film extending 2 mm. below the surface peripherally, where there were browning and brushlike mycelium. There was a small amount of mycelial fuzz below the growth plate. (Growth, 4 plus.)

On Sk the surface growth was white; it was much more flattened than on S. The growth plate was well demarcated 2 mm. below the surface; it dipped to 4 mm. at its edge, and there was fuzzy mycelium below. (Growth, 2 plus.)

On H there was a bit of growth at the plant. The growth plate was 5 mm. below the surface; it dipped to 8 mm. peripherally and was crescentic. It was light brown, especially centrally, and was well demarcated. (Growth, 2 plus.)

On C there was no growth.

*Endomyces Capsulatus.*—On S there was a thin mycelial down covering the slant, the surface of which was slightly irregular. Peripherally there was frosting with a subsurface dip of 4 mm. (Growth, 4 plus.)

On Sk the surface was smooth with a sparse but well demarcated bit of growth. On the growth plate, which was 3 mm. below the surface, there was white subsurface growth. The growth thinned out at the edge, which dipped to 5 mm., and was opaque centrally. (Growth, 3 plus.)

On H the growth extended 7 mm. below the surface from the surface plant. There was no definite growth plate. (Growth, 2 plus.)

On C a bit of waxy growth on the surface extended 5 mm. below the surface. (Growth, 2 plus.)

*Endomyces Dermatitidis.*—On S there was a woolly mycelial growth covering the surface. The growth plate was 1 mm. below the surface and dipped about 3 mm. at its edge. (Growth, 4 plus.)

On Sk there was a sparse white mycelium on the surface. The plate of growth was 3 mm. below the surface, dipping to 7 mm. at its edge. (Growth, 4 plus.)

On H there was a faintly noticeable growth on the surface. The subsurface growth was uniform and mycelial, blended into the medium peripherally and was 6 mm. deep. (Growth, 2 plus.)

On C the growth was like that on H.

*Epidermophyton Cruris.*—On S there was an olive-tinted surface mycelium 4 mm. thick with a slight amount of powder. There was no subsurface mycelium in evidence. (Growth, 5 plus.)

On Sk the surface powdery mycelium was 1 mm. thick; the surface was slightly irregular. The growth plate was 1 mm. below the surface, extending to 5 mm. at its edge; it was well demarcated and had a scraggly growth projecting from the plate into the medium. At the edge of the plate were treelike mycelia extending into the medium peripherally. (Growth, 4 plus.)

On H there was a sparse tan mycelium on the surface. The growth plate was 2 mm. below the surface; it dipped at the edge to 8 mm., and there was some browning centrally. (Growth, 3 plus.)

On C there was a sparse film of growth on the surface. The growth plate was 2 mm. below the surface and was almost transparent. (Growth, 2 plus.)

*Epidermophyton Inguinale.*—On S there was a wrinkled white powdery surface growth with only a slight amount of subsurface fuzz and a subsurface dip of 4 mm. peripherally. (Growth, 5 plus.)

On Sk there was a scant smooth white powdery growth on the surface. The subsurface plate was sunk 2 mm. and showed slight fuzz below and cottony rootlets at the edge, where it dipped 6 mm. (Growth, 4 plus.)

On H there was a low surface mycelium over the plant, with slight browning below. There was a well delimited crescentic plate of growth 6 mm. below the surface, dipping at its edge, where a few cottony rootlets were present. (Growth, 3 plus.)

On C there was a bit of fuzz on the surface, which was tinted yellow. The plate of growth was 2 mm. below the surface. (Growth, 2 plus.)

*Epidermophyton Rubrum.*—On S there was a white surface mycelium. The growth extended to 1 cm. below the surface peripherally. The plate of growth was of port wine color, and the medium below was pigmented. A sparse fuzz of mycelium extended into the medium from the plate. (Growth, 5 plus.)

On Sk there was a white mycelium on the surface, with a light yellow plate of growth sunk about 1 mm. below the surface. (Growth, 4 plus.)

On H there was a white mycelium resembling a powder puff at the plant. The plate of growth was well demarcated; it was 3 mm. below the surface, was opaque and dipped peripherally. (Growth, 3 plus.)

On C there was a bit of mycelial fuzz on the surface. The plate of growth was 2 mm. below the surface and dipped slightly peripherally. Color was absent. (Growth, 2 plus.)

*Geotrichum Bachmann.*—On S there was a somewhat irregular waxy growth covering the surface. The growth plate was about 1 mm. below the surface and dipped slightly at its edge. There was a well demarcated light pink pigmentation of the lower portion. (Growth, 5 plus.)

On Sk there was a smooth, waxy surface. The growth plate was 2 mm. below the surface, dipping to 4 mm. at its edge. (Growth, 3 plus.)

On H the surface was slightly waxy and almost transparent. The growth plate was 4 mm. below the surface. (Growth, 2 plus.)

On C there were a sparse surface and subsurface growth. (Growth, 1 plus.)

*Glenospora Gammeli.*—On S there was a low faintly fawn-colored mycelium covering the surface. There was sparse subsurface fuzz under the growth, and dipping of 3 mm. was noted at its edge. (Growth, 4 plus.)

On Sk there was a light fuzz on the surface. The growth plate was 4 mm. below the surface and dipped 8 mm. at its edge. (Growth, 3 plus.)

On H there was no noticeable surface growth. The subsurface growth was the color of the medium and blended with it, extending into the medium about 5 mm. There was no growth plate. (Growth, 2 plus.)

On C the culture was like that on H.

*Indiella Americana.*—On S the surface mycelium was olive tinted and like doe skin and had a few radii centrally. The plate extended 1 mm. below the surface and was a bit fuzzy below, dipping 3 mm. at its edge, where the mycelium was fine and lacelike. The subsurface growth was delimited peripherally. (Growth, 4 plus.)

On Sk there was a sparse fuzz at the plant on the surface. The growth plate was tinted brownish green, was 3 mm. below the surface and dipped 6 mm. below the surface peripherally. (Growth, 3 plus.)

On H there was no noticeable surface growth. A hairlike white subsurface mycelial growth with an apex of growth toward the surface extended 6 mm. into the medium, but there was no definite plate. (Growth, 2 plus.)

On C the culture was like that on H.

*Lichtheimia sp.*—On S there was profuse mycelium, filling the tube adjacent to the medium. (Growth, 5 plus.)

On Sk the plate of growth was 2 mm. below the surface, was poorly developed, and possessed a mycelial surface extending above the medium aerially. (Growth, 5 plus.)

On H there was a sparse mycelium on the surface, with sparse strands extending 5 mm. into the medium. (Growth, 1 plus.)

On C there was a suggestion of sparse mycelium in the medium.

*Microsporon Audouini.*—On S the surface growth was smooth light fawn-colored downy mycelium resembling doe skin. The growth plate was 1 mm. below the surface and dipped 4 mm. at its edge. There was a yellowish brown tint to the plate. (Growth, 5 plus.)

On Sk there was a sparse powdery growth on the surface. The plate was 2 mm. below the surface and had a reddish brick dust hue, little of which was imparted to the medium. There were mycelial streamers extending peripherally from the plant. (Growth, 4 plus.)

On H there was a sparse bit of growth at the plant. The plate of growth was 3 mm. below the surface and of a reddish brick dust color. (Growth, 3 plus.)

On C there was a small amount of white mycelium on the surface. The plate of growth was 3 mm. below the surface and faintly pink. (Growth, 3 plus.)

*Microsporon Felineum.*—On S the surface was slightly nodular and covered with a soft, velvet-like white mycelium. At the edge there was a subsurface dip of about 3 mm.

On Sk the surface was smooth with sparse mycelium, especially at the plant. The growth plate was 2 mm. below the surface, dipping to 6 mm. at its edge, from which brushlike mycelium extended peripherally. (Growth, 3 plus.)

On H the mycelial growth at the plant sent feelers to the glass. The plate was 3 mm. below the surface and extended to 6 mm. below the surface peripherally. (Growth, 3 plus.)

On C there was a sparse bit of growth at the plant, with faint browning. The growth plate was 4 mm. below the surface. (Growth, 3 plus.)

*Microsporon Gypseum.*—On S there was a white surface mycelium with a brownish base. There was no noticeable subsurface mycelium. (Growth, 5 plus.)

On Sk there was a thin white surface mycelium. The growth plate was from 2 mm. below the surface centrally to 3 mm. peripherally. (Growth, 4 plus.)

On H there was a sparse mycelium on the surface. The growth plate was 3 mm. below the surface, dipping to 7 mm. peripherally; it was of a brilliant rusty color. This subsurface mycelial growth seemed to stream out peripherally. (Growth, 3 plus.)

On C there was a sparse bit of growth at the plant centrally. The subsurface plate with its rusty color was similar to that on H. Apparently in both instances a slight amount of pigment was imparted to the medium. (Growth, 3 plus.)

*Monilia Albicans.*—On S the growth was demarcated equally well on and below the surface. There was a scrambled egg type of growth on the surface centrally. There was a subsurface dip of 5 mm. peripherally, but a cottony subsurface growth extended to a depth of 1 cm. A few short dendritic processes projected peripherally. (Growth, 5 plus.)

On Sk there was much less surface than subsurface growth. The subsurface mycelium was well demarcated, more discrete, thicker and more compact than on S; there were a coral-like formation and a plate of growth 2 mm. below the surface. (Growth, 4 plus.)

On H there was little surface growth centrally. The plate of growth was well demarcated 3 mm. below the surface. From it thick subsurface mycelium extended 1.5 cm. into the medium. (Growth, 2 plus.)

On C the growth was largely below the surface except at the plant. (Growth, 1 plus.)

*Monosporium Apiospermum.*—On S there was a white surface mycelium about 3 mm. thick with a slight subsurface dip at its edge. There was black coloration at the base of the growth, especially peripherally. (Growth, 5 plus.)

On Sk the surface mycelium was thin. The black coloration was not as evident as on S. The plate of growth was 3 mm. below the surface and slightly deeper at its edge. (Growth, 4 plus.)

On H there was a sparse amount of surface growth at the plant. The plate of growth was 5 mm. below the surface; it was opaque, especially centrally, and had a faint black color. (Growth, 3 plus.)

On C there was no growth on the surface. The plate was 3 mm. below the surface, where there was a slight black line of demarcation; its edge blended into the medium. (Growth, 3 plus.)

*Oospora Humi.*—On S there was a wet, waxy mycelial surface growth with a thin layer of dry white mycelium. Its edge was slightly below the surface. (Growth, 5 plus.)

On Sk the growth extended to about 1 mm. below the surface centrally and 3 mm. peripherally. (Growth, 4 plus.)

On H there is no appreciable surface growth. The plate of growth was 3 mm. below the surface centrally and 5 mm. below peripherally; it was the color of the medium and made up of interlaced mycelia. (Growth, 2 plus.)

On C the growth had a waxy surface but was not as far below the face as on H. (Growth, 2 plus.)

*Scopulariopsis Brevicaulis.*—On S there was a brownish powdery mycelial growth with a subsurface fuzz extending 7 mm. into the medium. (Growth, 5 plus.)

On Sk the surface growth was less powdery than on S. The subsurface fuzz was larger, and the plate of growth was 2 mm. below the surface. (Growth, 5 plus.)

On H the surface growth was sparser but more mycelial and of lighter color than on Sk. The medium below the surface growth was occupied by mycelium. There was no definite growth plate. (Growth, 3 plus.)

On C the surface growth was waxy, was mostly subsurface and extended through the medium. (Growth, 3 plus.)

*Sporotrichum Schenckii.*—On S there was a waxy surface growth, which was rough and sandpapery centrally, and well demarcated and the edge of which dipped 3 mm. below the surface. (Growth, 5 plus.)

On Sk there was a sparse smooth, waxy surface growth. The growth plate was 2 mm. below the surface centrally, was well demarcated and dipped to 6 mm. peripherally. (Growth, 4 plus.)

On H there was no appreciable surface growth. The growth plate was crescentic, well demarcated and 5 mm. below the surface, dipping to 1 cm. at its edge. (Growth, 3 plus.)

On C the growth was similar to that on H but was less well demarcated. (Growth, 2 plus.)

*Trichophyton Balcaneum.*—On S there was a waxy growth over the slant, with central radii. The plate of growth was 2 mm. below the surface, dipping to 4 mm. at its edge. (Growth, 4 plus.)

On Sk there was no noticeable surface growth. The plate was 4 mm. below the surface and had a whitish surface. It was opaque, was well demarcated peripherally and had fine treelike mycelia projecting outward. (Growth, 3 plus.)

On H there was no noticeable surface growth. The subsurface growth was well demarcated, extending to a depth of 8 mm. and dipping more at its edge. The mycelium had its apex toward the surface and had the appearance of a subsurface powder puff. (Growth, 2 plus.)

On C there was no noticeable surface growth. The subsurface growth extended 4 mm. in depth. (Growth, 1 plus.)

*Trichophyton Crateriforme.*—On S there was a somewhat mortised, much wrinkled powdery surface growth with a tint of pink. The plate of growth was 1 mm. below the surface and dipped to 4 mm. peripherally. There was a brown base, and some color was imparted to the medium. A few subsurface rootlets of mycelium extended peripherally. (Growth, 5 plus.)

On Sk practically all wrinkling was gone. There was a thin layer of surface mycelium with yellowish powder centrally. The plate of growth was 3 mm. below the surface. Its base was yellowish brown. The growth was well demarcated, and subsurface rootlets at the periphery were treelike. (Growth, 4 plus.)

On H the only surface growth was a yellowish powder at the plant. The plate of growth was 3 mm. below the surface and had a brownish yellow coloration, especially near the plant. The plate was well demarcated, with fine rootlets peripherally. (Growth, 3 plus.)

On C there was a thin powdery surface growth, especially at the plant. The plate was 3 mm. below the surface. The only pigmentation was a bit of brown at the plant. (Growth, 3 plus.)

*Trichophyton Decalvans.*—On S there was a low white mycelium on the surface. The growth plate was 1 mm. below the surface, dipped to 5 mm. at its edge and was well demarcated. (Growth, 5 plus.)

On Sk there was a sparse suggestion of mycelium on the surface. The growth plate was 3 mm. below the surface, dipping somewhat at its edge. (Growth, 3 plus.)

On H there was no growth.

On C there was no growth.

*Trichophyton Granulosum.*—On S there was a soft compact surface mycelium tinted pink in areas with streamers to the side of the tube. The base of the growth and especially the edge showed port wine to brown pigment. There was practically no subsurface mycelium. (Growth, 5 plus.)

On Sk there was a low soft white surface mycelium. The growth plate was 2 mm. and dipped to 3 mm. below the surface peripherally. (Growth, 4 plus.)

On H there was a sparse surface mycelium. The growth plate was amber colored, was 4 mm. below the surface centrally and dipped to 6 mm. at its edge. (Growth, 3 plus.)

On C there was a thin layer of cream-colored powdery mycelium on the surface. The growth plate was 4 mm. below the surface and had a faint greenish tint. (Growth, 3 plus.)

*Trichophyton Gypseum.*—On S there was a compact white mycelial surface, somewhat irregular and cratered centrally. The plate of growth was 2 mm. below the surface centrally and 3 mm. below peripherally. (Growth, 5 plus.)

On Sk the surface growth was smooth, with a thin layer of compact white mycelium. The plate of growth was 2 mm. below the surface centrally and 3 mm. below peripherally. (Growth, 4 plus.)

On H there were sparse bits of mycelium on the surface, especially at the plant. The plate was 4 mm. below the surface, dipped slightly at its edge and was somewhat opaque. The growth was slightly browner at the plant. (Growth, 2 plus.)

On C the subsurface growth was hard to distinguish but extended to 4 mm. below the surface and possessed a light yellow tint. (Growth, 1 plus.)

*Trichophyton Gypseum-Asteroides.*—On S there was a low soft powdery surface mycelium, slightly wrinkled, with a port wine base, dipping 2 mm. below the surface peripherally. (Growth, 5 plus.)

On Sk there was a thin, smoother surface mycelial covering, which dipped 3 mm. below the surface at the edge. (Growth, 4 plus.)

On H there was the faintest sprinkling of surface mycelium especially at the plant. The growth plate was 3 mm. below the surface centrally and 7 mm. below peripherally and had a brownish edge. (Growth, 3 plus.)

On C there were thin white mycelium at the plant centrally and a light amber-colored subsurface growth similar to that on H. (Growth, 2 plus.)

*Trichophyton Gypseum-Lacticolor.*—On S there was a thick white surface mycelium with practically no dipping at its edge. (Growth, 5 plus.)

On Sk the surface mycelium showed slight dipping at its edge. The growth was slightly deeper than that on S. (Growth, 5 plus.)

On H there was a slight amount of white mycelium on the surface, especially at the plant. The growth plate was 4 mm. below the surface and dipped somewhat at its edge. (Growth, 3 plus.)

On C there was a slight amount of white mycelium at the surface. The growth plate was 3 mm. below the surface. (Growth, 3 plus.)

*Trichophyton Interdigitale.*—On S the surface mycelium was compact and 3 mm. thick. There was no noticeable subsurface growth. (Growth, 5 plus.)

On Sk there was a slight subsurface sinking of growth at the edge.

On H the surface growth was thin, especially near the plant. The growth plate was 2 mm. below the surface centrally and 5 mm. below peripherally. (Growth, 3 plus.)

On C there was a thin film of surface growth. The growth plate was 1 mm. below the surface. (Growth, 2 plus.)

*Trichophyton Japonicum.*—On S there was a thin slightly tan surface mycelial growth. The medium and the base were tan to pink, and the growth dipped 2 mm. below the surface at its edge. The growth in some cultures showed a frosted mycelial surface with a light tan tint. (Growth, 4 plus.)

On Sk there was a sparse slightly powdery or frosted growth on the surface. The growth plate was from 1 mm. below the surface centrally to 3 mm. below peripherally and had a light brownish pigmentation. (Growth, 3 plus.)

On H there was no noticeable surface growth. The growth plate was brownish, 5 mm. below the surface, opaque, cottony and not clearcut. (Growth, 2 plus.)

On C there was no growth.

*Trichophyton Louisianicum.*—On S there was a low smooth fawn-colored soft surface mycelium extending about 1 mm. below the surface. The growth plate was caramel colored and dipped about 4 mm. at its edge. There was a short fuzzy mycelium below the plate. (Growth, 5 plus.)

On Sk there was a thin white fuzzy mycelium on the surface. The plate was 3 mm. below the surface, dipped slightly at its edge and was of a red brick dust color; mycelium streamed from it into the medium peripherally. (Growth, 4 plus.)

On H there was no noticeable growth on the surface. The plate was 4 mm. below the surface, had a red brick dust color and dipped slightly at its edge. The growth seemed to stream out from the plant. (Growth, 3 plus.)

On C there was a thin white mycelial fuzz on the surface. The plate was 2 mm. below the surface and showed a slight amount of red brick dust color. (Growth, 3 plus.)

*Trichophyton Niveum.*—On S the mycelial surface mat was 4 mm. thick and showed a slight subsurface dip at its edge. (Growth, 5 plus.)

The growth on Sk had less aerial mycelium than that on S. The plate was about 2 mm. below the surface and had a slightly greater dip at its edge. (Growth, 4 plus.)

On H there was a sparse surface mycelium at the plant. The plate with its white surface was 3 mm. below the surface and at its edge dipped to 7 mm. (Growth, 3 plus.)

On C there was a bit of mycelium at the plant. There was sparse growth 2 mm. below the surface. It was almost translucent. (Growth, 2 plus.)

*Trichophyton Purpureum.*—On S there was a compact downy surface mycelium of port wine color. The base and the medium were from brown to port wine color. There was little subsurface growth. (Growth, 5 plus.)

On Sk there was a compact white surface mycelium. The growth sank 5 mm. below the surface peripherally. Pigment was absent. (Growth, 4 plus.)

On H there was a sparse white surface mycelium which had a brownish tint centrally. The growth plate was 2 mm. below the surface, dipped somewhat at the edge and was amber tinted. (Growth, 2 plus.)

On C there was a sparse cream-colored surface mycelium. The plate was 2 mm. below the surface. There was a slight brown tint to the plate. (Growth, 2 plus.)

*Trichophyton Sulfureum.*—On S the surface growth was irregular, folded and depressed centrally and had a low powdery mycelium. It dipped below the surface to 5 mm. at its edge. (Growth, 5 plus.)

On Sk the surface was a low smooth light tan powdery mycelium. The growth plate was 2 mm. below the surface, dipping to 6 mm. peripherally. (Growth, 4 plus.)

On H there was a sparse bit of surface growth. The growth plate was comparatively opaque; it was 3 mm. below the surface centrally and 8 mm. below at its edge. There was slight browning centrally, and branched mycelium extended peripherally from it. (Growth, 3 plus.)

On C there was a sparse powdery growth on the surface, especially at the plant. The growth plate was 2 mm. below the surface centrally and 8 mm. below peripherally; it was distinct and of faint olive tint. (Growth, 3 plus.)

*Willia Anomala.*—On S there was a well demarcated waxy surface growth extending to 3 mm. below the surface. The plate of growth was 1 mm. below the surface. (Growth, 3 plus.)

On Sk there were a 1 cm. waxy growth on the surface and a subsurface growth 2 cm. in diameter. The subsurface growth was well demarcated, dipping down 5 mm. at its edge, where there were short branched rootlets peripherally. The plate was 2 mm. below the surface. (Growth, 2 plus.)

On H there was a small amount of growth on the surface centrally. The remainder was a compact subsurface growth. (Growth, 1 plus.)

On C the growth was like that on H.

RÉSUMÉ

It will be noted that the depth of the growths below the surface increased with various mediums in the following order: peptone, pig skin and hair. The amount of cysteine-cystine increased in like order. The growth on the cysteine was predominantly below the surface and in some instances so much like that on hair medium that this amino-acid appeared to be the sole source of nitrogen.

In order to determine whether or not cysteine was the sole cause of subsurface growth in pig skin medium, the Difco Laboratories, Inc., hydrolyzed pig skin in an alkaline medium. As a result no test was made for cysteine, cystine or arginine. Growth on this medium was markedly subsurface, apparently indicating that cysteine is not the only factor with relation to subsurface growth on pig skin medium. This seems probable since other amino-acids give marked subsurface growth. A medium containing 1 per cent peptone or 0.25 per cent peptone and 4 per cent dextrose also gives much subsurface growth.

With reference to tests for cystine and cysteine it may be said that knowledge concerning both of these substances is so chaotic that it is dangerous to draw definite conclusions. I feel that I can assume that the cysteine and the cystine were removed from the pig skin and that possibly the chemical and physical state existing in the medium as a result of the source and proportions of carbon and nitrogen are important factors in subsurface growth.

That other micro-organisms might grow on blood agar as a plate several millimeters below the surface was made evident when I isolated a streptococcus from the throat of a patient with chronic arthritis. While this organism would probably fall in the class of streptococci with anaerobic tendencies, this study of pathogenic fungi permits one to conclude that other factors were involved.

There is evidence that cysteine is inhibitory for aerobic bacteria.[2] It has been used for reducing oxygen tension in mediums. Workers[3]

2. Brunsting, L. A., and Simonsen, D. G.: Cutaneous Ulcers Treated by Sulphydryl Containing Amino-Acid Cysteine, J. A. M. A. **101**:1937 (Dec. 16) 1933.

3. (*a*) Hammett, F. S.: Interpretation of Malignant Growth Based on Chemistry of Cell Division, Arch. Path. **8**:575 (Oct.) 1929; Protoplasma **7**:297, 1929. (*b*) Hammett, F. S., and Reimann, S. P.: J. Exper. Med. **50**:445, 1929; Proc. Soc. Exper. Biol. & Med. **27**:20, 1929. (*c*) Reimann, S. P.: Use and Reasons for the Use of Thiocresol to Stimulate Wound Healing, J. A. M. A. **94**:1369 (May 3) 1930.

have emphasized the importance of reduced sulfhydryl in stimulating healing of wounds by increasing cell mitosis. In these experiments time was not allowed for cysteine to revert to cystine, which is inactive, before renewal of the solution. There is work in progress indicating that the curve of activity in the transformation of cysteine to cystine or/and other end-products extends over a period of from thirty-six hours to two or more weeks, the time increasing with the increase in acidity and concentration of the cysteine in solution. The reduced sulfhydryls, with the exception of cysteine and compounds containing antiseptics in combination, stimulate bacterial growth.[4]

Because of the high cysteine-cystine content of hair, the comparatively high cysteine-cystine content of skin and the invasion of the medium, one wonders what part cysteine-cystine plays in the production of the subsurface growth. Since other amino-acids act similarly, the ratio of carbon to nitrogen with relation to a certain state must be important. This state will result when peptone alone or a combination of 0.25 per cent peptone and 4 per cent dextrose is used. In a future paper I shall discuss the fact that sodium phosphate in the medium converts certain subsurface growths to surface growths and that a combination of sodium phosphate and sodium lactate adds to the number of cultures in which a change from subsurface to surface growth is observed. This may further aid in clarifying the state of affairs in regard to subsurface growth.

## SECTION II

In this study I wished to determine whether stabs of bits of growth from 2 to 3 cm. in the medium would show decided growth when hydrolyzed hair was used as an ingredient instead of peptone. The following mediums were used: (1) Sabouraud's proof medium; (2) hydrolyzed women's hair medium (1 per cent hydrolyzed hair, 4 per cent dextrose, 1.5 per cent agar), and (3) W medium. All were adjusted to 5.6 $p_H$ and incubated at room temperature in diffused light for forty days.

I shall not describe the types of growth. Suffice it to say they showed distinctive surface structures. With reference to the deep stab, there seemed to be no noticeably great tendency to grow about this plant. With hydrolyzed hair medium there was a tendency for subsurface growth to appear, as described. In general, there were less "takes" on the medium prepared from hydrolyzed hair of women than on that prepared from hydrolyzed hair of children.

4. Brunsting and Simonsen.[2] Reimann.[3c]

While growths were subsurface on hydrolyzed hair medium, a tendency for growth to develop around stabs deep in the medium was not present to any noticeable degree. Possibly mycelial communication to the surface is a factor of importance in the subsurface growths as they do occur.

SECTION III

Since some of the cysteine mediums prepared with 1.5 per cent agar were not as solid as peptone mediums prepared with like amount of agar, it was necessary to make up Sabouraud's proof medium of varying solidity in order to see whether this was a factor in subsurface growth. Sabouraud's proof medium with the following concentrations of agar was used: 0.5 per cent, 1 per cent, 1.5 per cent, 3 per cent and 6 per cent. When 0.5 per cent agar was used the medium was less solid than any of the slants in which cysteine was used.

The growths on the mediums with lesser concentrations of agar were wetter and slightly more prolific, but the growths on all the mediums were comparatively similar morphologically. There was no appreciable sinking of the growth or increase in subsurface mycelium with the lower concentrations. Waxy growths on low concentration showed a tendency to take on white mycelium on higher concentrations, to spread less and in some instances to take on more powder. On 3 and 6 per cent agar the following organisms were drier and had more radial or irregular surface: Candida candida, Monilia albicans, Sporotrichum Schenckii, Trichophyton crateriforme, Trichophyton sulfureum. In the 6 per cent agar preparation mycelium usually appeared more compact.

Apparently the lesser degree of solidity of cysteine medium does not account for the subsurface growth.

SECTION IV

In this study I attempted to determine whether cysteine in Sabouraud's proof medium would result in a more subsurface growth. The mediums used were: (1) Sabouraud's proof medium; (2) Sabouraud's proof medium containing 0.25 per cent cysteine, and (3) a medium containing 0.25 per cent cysteine hydrochloride, 4 per cent dextrose and 1.5 per cent agar. The mediums were adjusted to 5.6. The growths took place at room temperature in diffused light for forty days.

Growths on the cysteine medium were subsurface in type and similar to those already described. With the Sabouraud medium containing cysteine (CS) there was a suggestion of sinking only in certain instances. The growth on the surface was similar to that on Sabouraud's medium except that when CS medium was used marked changes, as follows, were observed:

Achorion Schoenleinii was more wrinkled centrally. Candida candida showed short spicules on a wrinkled surface growth. Endodermophyton tropicale was flatter, irregular, wrinkled, more waxy and not as mycelial. Endodermophyton indicum was a raised lump of finely scrambled waxy tan growth. Endomyces capsulatus and Endomyces dermatitidis lacked the waxiness which was observed on S, showed low mycelium and were more delimited. Epidermophyton cruris was an irregularly scrambled growth covered with sulfur-colored powder and low mycelium. Epidermophyton inguinale was a scrambled, wormlike surface growth raised centrally and covered with downy white mycelium. Epidermophyton rubrum was a compact white mycelial growth with a base showing slightly pink but not approaching the port wine color noted on S. Geotrichum Bachmann showed a deeper pink tint; Indiella americana was more delimited. Microsporon Audouini was more radial and less mycelial and showed more suggestion of powder. Microsporon felineum was more irregularly radiate and its surface was covered with powder instead of with low downy mycelium. Monosporium apiospermum was more delimited. Monilia albicans had fine wormlike and scrambled surface radii covered with low spicules, whereas on S there was a scrambled surface growth. Scopulariopsis brevicaulis had lost much of the brown pigmentation and showed a leaning toward matted white mycelium. Trichophyton balcaneum showed many fine wortlike radii of waxy brown growth, whereas on S the growth was smooth and waxy. Trichophyton crateriforme was more wrinkled, profuse and folded on itself. Trichophyton decalvans was irregularly radiate and somewhat translucent with a thin film of mycelium. Trichophyton granulosum had a more irregular, powdery surface tinted a rusty color with a reddish pink base, whereas on S it showed a pink color. Trichophyton gypseum showed a finely irregular wrinkled surface growth practically devoid of mycelium with some pink powder, whereas on S it had a compact white surface mycelium. The upper half of the growth of Trichophyton gypseum-lacticolor was wrinkled and covered with a brownish pink powder, while the lower half was covered with low white mycelium and the base was a deep port wine color; on S the growth was covered with mycelium with sparse areas of pink pigment. One strain of Trichophyton interdigitale showed a more irregular surface with some pink powder. Trichophyton japonicum showed some tan powder but centrally compact mycelium. Trichopyton louisianicum showed thicker and whiter mycelium. Trichophyton niveum showed a more irregular surface. Trichophyton purpureum showed a more irregular surface which instead of being of port wine color was light yellow. Trichophyton sulfureum showed a canary yellow powder. Willia anomala had a well delimited centrally waxy growth at first and later showed a white powdery and peripherally waxy growth.

While it cannot be said that the addition of cysteine to Sabouraud's medium resulted in a definitely more subsurface growth, there was indication from these observations that in certain instances it reduced gross pleomorphism and resulted in more differentiation of growth.

SECTION V

In this study, because of the fact that cysteine decomposes more readily in alkaline solutions, the $p_H$ of the mediums was varied. The mediums used were cysteine hydrochloride 0.25 per cent, dextrose 4

per cent, and agar 1.5 per cent adjusted to $p_H$ 5.6, 6.6 and 7.6. As a result of autoclaving the $p_H$ of the cysteine medium was reduced to 5.4, 6.1 and 6.6, respectively.

In general, the variations on Sabouraud's mediums could be attributed to natural variation of the organisms. On the cysteine mediums most organisms were slightly more delimited in the more acid medium and slightly more spread over the subsurface; in the more alkaline mediums they were profuse and in certain cases showed more surface growth. Amber pigment was especially noticeable when the more alkaline medium was used in culturing Scopulariopsis brevicaulis (brown surface powder being in evidence), Microsporon gypseum, Trichophyton granulosum, Trichophyton gypseum-asteroides, Trichophyton crateriforme and Trichophyton sulfureum. Monosporium apiospermum seemed to lose its black pigment in the more alkaline medium. On the more alkaline mediums there was less growth of Endomermophyton tropicale and Acladium Castellani.

These observations show changes which may be attributable to the cystine-cysteine ratio or to the resultant end-products. Similar studies in which glutamic acid was substituted for cysteine in mediums adjusted to $p_H$ 6, 7 and 8 showed similar growths for the respective organisms.

## COMMENT

Observations indicate that cysteine-cystine or derivatives therefrom can and do support micro-organismal growth below the surface. The depth of invasion when a 6 cm. depth of medium was used was usually within 1.5 cm. of the surface. Why these depths are preferred to the surface or to deeper ones could be answered only by complicated physicochemical studies. When 0.001 per cent methylene blue or 0.002 per cent indigo carmine [5] was added to a cysteine stab and the preparation was autoclaved, the dye was reduced to the leuko form. Within twelve hours color first forming on the surface sank to within 1.5 cm. of the surface, forming at its base a more intense dye line. This was difficult to explain by concentration of the dye, since when the base of the tube was broken color formed there. As noted, the growths observed in this study did not sink more than 1.5 cm. into the medium. Possibly similar physicochemical properties are responsible for both events. As time went on additional lines of decreasing intensity formed below the original dye line. These were similar to Liesegang rings and often seemed to emphasize the original dye line as a probable point of departure of diffusion possibly of active oxygen.

5. Williams, J. W.: Allergy, Immunity and Growth of Pathogenic Fungi in Vivo and in Vitro, Urol. & Cutan. Rev. **41**:117 and 198, 1937; footnote 1.

The medium containing 0.25 per cent cysteine was employed since there was considerable precipitate after the preparation had been autoclaved when 1 per cent cysteine was used. There was also a precipitate in the 0.25 per cent cysteine mediums of $p_H$ 5.4, but those of $p_H$ 6.1 and 6.66 were practically free from precipitate. The growths corresponded in type. On 1 per cent cysteine mediums there was no growth of Endodermophyton tropicale, no apparent growth of Lichtheimia sp., and on 1 per cent cysteine medium or on hair medium there was no growth of Trichophyton decalvans. On the 0.25 per cent cysteine medium containing 4 per cent dextrose and 1.5 per cent agar the growths were as follows: Endodermophyton tropicale showed a 1 plus growth predominantly below the surface, with no definite growth plate. Lichtheimia sp. showed a 1 plus growth with sparse mycelium on the surface and a suggestion of a growth plate 2 mm. below the surface; when the $p_H$ was raised to 6.6, however, the growth plate became more definite and was 4 mm. below the surface, and the growth was 2 plus. The growth of Trichophyton decalvans was 2 plus and subsurface, with no definite growth plate; when the method described in section II was used there was a sparse subsurface growth on the hair medium.

Since the surface tension and the osmotic pressure of the mediums used fell within the range of those associated with good growths, they are not discussed here. Much more extensive work would have to be done in order to consider all the possible variables.

## CONCLUSIONS

Descriptions of growths on cysteine-cystine mediums are given, and a comparison is made with growths on other mediums.

Growths on hydrolyzed hair and on hydrolyzed pig skin mediums were studied, and the depth of subsurface growth appeared to vary with the cysteine-cystine content of the medium, whereas the surface growth appeared to be dependent on other constituents.

The fact that the subsurface growths on cysteine-cystine mediums did not usually extend more than 1.5 cm. into the medium is correlated with observations on methylene blue and indigo carmine dye lines in mediums allowed to solidify at room temperature.

Around stabs from 2 to 3 cm. in the medium there was little if any growth, indicating a condition at this depth different from that of the surface portion of the medium.

The solidity of the medium seemed unimportant in making growths more subsurface over a range made possible by the use of from 0.5 to 6 per cent agar.

Cysteine-cystine in Sabouraud's proof medium seemed to increase differentiation in certain instances but had little effect on making the growth more subsurface.

An increase in the $p_H$ of the cysteine medium from 5.4 to 6.6 seemed in many instances to increase the amount of growth slightly. The growths in the more alkaline mediums were slightly more diffuse through the subsurface reducing delimitation.

Apparently the subsurface growth on the pig skin medium was not dependent on cysteine-cystine alone, since it resulted when this ingredient was apparently removed.

The observations of subsurface growth have emphasized a new field for differentiation of pathogenic fungi. When grown on plates or slants many of the organisms showed specific characteristics.

# BENIGN HEPATITIS OF EARLY SYPHILIS

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Three undoubted cases of benign hepatitis of early syphilis and 1 probable one are presented from the United States Public Health Service Venereal Disease Clinic, Hot Springs, Ark., because such cases are rare. Three of the patients had secondary syphilitic lesions of the skin or mucous membranes, and 1 had a primary lesion. Two of them showed a Herxheimer reaction when treatment was begun with neoarsphenamine. The jaundice in all 4 cases disappeared promptly under treatment for syphilis.

## INCIDENCE

Only the 4 previously mentioned cases of benign hepatitis of early syphilis have been recorded at the clinic during the five years from 1931 to 1935, making an incidence of 4 cases among 4,820 cases of recent syphilis (syphilis of one year's duration or less), or 1 case among 1,200, as follows:

| | White | | | Negro | | | White and Negro |
|---|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total | |
| Primary | 921 | 83 | 1,004 | 191 | 17 | 208 | 1,212 |
| Secondary | 817 | 412 | 1,229 | 184 | 60 | 244 | 1,473 |
| Latent or one year's duration or less | 1,353 | 381 | 1,734 | 302 | 99 | 401 | 2,135 |
| | 3,091 | 876 | 3,967 | 677 | 176 | 853 | 4,820 |

Three of the patients were admitted to the clinic within a period of five weeks.

Moore [1] stated that he had observed only 3 or 4 cases of benign hepatitis of early syphilis and that benign hepatitis occurs not oftener than in 1 of 1,000 persons recently infected with syphilis. Stokes [2] said he had observed only 1 undoubted case of benign hepatitis in a survey of 300 patients with early syphilis. The incidence of the condition was stated by Wile [3] to be below 1 per cent, by Werner [3] to be 0.37 per cent and by Reimer [3] to be 3 per cent.

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From the United States Public Health Service Venereal Disease Clinic, Hot Springs, Ark.

1. Moore, J. E.: Modern Treatment of Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

2. Stokes, J. H.: Modern Clinical Syphilology: Diagnosis, Treatment and Case Studies, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

3. Cited by Elliott and Todd.[5]

### CLASSIFICATION OF SYPHILIS OF THE LIVER

Syphilis of the liver has been classified in the paper of O'Leary, Greene and Rowntree [4] in the following manner: (1) early acute benign hepatitis, (2) syphilitic destructive hepatitis, or acute yellow atrophy, (3) subthreshold hepatic syphilis detected by functional tests, (4) hepatorecurrence, (5) mild chronic hepatitis of latent syphilis, (6) diffuse and localized gummatous hepatitis, (7) chronic interstitial pericellular cirrhosis of heredosyphilis and (8) perihepatitis.

### THE PATHOLOGIC PICTURE

There is no record of any patient with benign hepatitis of early syphilis coming to autopsy. Stokes [2] stated that it is believed that there are possibly a diffuse inflammatory factor and a proliferative element in the pathologic picture. Other conjectures as to the cause of the jaundice have included roseola of the bile ducts, condyloma of the ampulla and pressure from enlarged glands in the portal fissure.

### CLINICAL PICTURE

Stokes [2] stated that early acute benign hepatitis is a rare complication of the florid eruptive state of syphilis. The chief symptom is jaundice, and the chief sign is enlargement of the liver. He further said that benign hepatitis of early syphilis is distinguished with difficulty from intercurrent catarrhal jaundice of nonsyphilitic origin and from hepatorecurrence. Differentiation must rest entirely on (1) the presence of a chancre or secondary eruption (usually roseola), (2) a Herxheimer reaction, if treatment is begun with an arsphenamine preparation, and (3) prompt cure, if treatment is continued. From two to five weeks should be sufficient for complete recovery of the patient with early hepatitis except when there is residual enlargement of the liver.

Elliott and Todd [5] presented a case of benign hepatitis of early syphilis which occurred two months after the appearance of the chancre. It was possible to follow the course of hepatic dysfunction by the icterus index. On the institution of treatment with a bismuth preparation, a Herxheimer reaction took place. By the icterus index they demonstrated this reaction as well as the ability of bismuth to produce it and the therapeutic test of the syphilitic nature of the hepatitis as described by Stokes.

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4. O'Leary, P. A.; Greene, C. H., and Rowntree, L. G.: The Various Types of Syphilis of the Liver, with Reference to Tests for Hepatic Function, Arch. Int. Med. **44**:155 (Aug.) 1929.

5. Elliott, J. A., and Todd, L. C.: Hepatitis of Early Syphilis: Blood Bilirubin Determinations as a Possible Aid in Diagnosis and as a Guide to Treatment; Report of a Case, Arch. Dermat. & Syph. **17**:299 (March) 1928.

## TREATMENT

There is a question in the minds of some as to the danger of disastrous results when a Herxheimer reaction occurs during treatment of a patient with benign hepatitis of early syphilis. There is no question of danger in my mind, after experience with the 4 cases previously mentioned, even if an arsphenamine preparation is used from the outset of treatment, provided it is used in small doses at first and the patient is carefully watched. Neoarsphenamine combined with bismuth was used from the outset in the treatment of 2 of my patients. The Herxheimer reactions which occurred in those 2 were not alarming. It is true, however, that no Herxheimer reaction occurred in the patient treated with bismuth alone and the patient to whom mercury benzoate was administered for the first three weeks of his treatment. Jaundice in the patient treated with bismuth alone subsided in seventeen days, as compared with periods of nineteen to twenty-five days, respectively, for the two patients treated with neoarsphenamine and bismuth combined. Jaundice disappeared in forty days in the case of the patient who received preliminary injections of mercury benzoate intramuscularly for three weeks, followed by arsphenamine and mercury benzoate combined. No trouble was encountered with any of the methods of treatment.

Moore [1] mentioned giving arsphenamine at the start of treatment to patients with benign hepatitis of early syphilis and said that there is no reason for caution in the use of arsphenamine.

Stokes [2] stated:

> The advent of bismuth has simplified the situation here, making it possible to treat these patients vigorously and at the same time fairly effectively so far as response of surface infectious lesions if present is concerned, until the return of the icterus index to normal. . . . Personally I believe it entirely safe at this point to resume or institute the use of an arsphenamine in moderate doses in the effort to secure a curative effect in early syphilis.

## REPORT OF CASES

CASE 1.—M. E. H., a woman aged 25, separated from her husband and the mother of two girls aged 6 and 4 years, respectively, was admitted to the clinic on April 17, 1935. She complained of genital lesions which had first come to her notice one week before admission, and of a cutaneous eruption and yellowing of the skin, which had begun about six weeks before. The patient stated that she had not previously had genital lesions, secondary cutaneous eruption or treatment for syphilis.

Physical examination showed her to be ambulatory, well nourished and not acutely ill. No genital ulcer or scar was seen. The genital lesions of which the patient complained were secondary lesions, i. e., eroded papules of both labia majora and labia minora, the perineum and the perianal region. A diffuse, symmetrical macular secondary eruption involved the face, both surfaces of the neck, the trunk, the arms, the forearms and the thighs and the dorsa of the hands. Deep secondary papules appeared on the palms and the soles. The skin and the conjunc-

tivae were very yellow. There was a general adenopathy. The edge of the liver was felt 2 fingerbreadths below the costal margin, and it was slightly tender. The spleen was not felt.

On April 17 the patient's reaction to the Kolmer and Kahn tests was 4 plus; her icterus index was 80. On April 18 urinalysis gave negative results except for bile. A diagnosis of maculopapular secondary syphilis with benign hepatitis was made.

Treatment consisted of seven doses of neoarsphenamine and one dose of arsphenamine (beginning with 0.01 Gm. of neoarsphenamine and increasing to 0.4 Gm.) and nine intramuscular doses of bismuth potassium tartrate (each dose containing 34 mg. of elemental bismuth) during the period from April 18 to May 7 inclusive. The only other measures of treatment were a diet low in fats and baths at Hot Springs six days per week.

There was no reaction noticeable to the patient after any of the first three small doses of neoarsphenamine.

On the night of April 22, after a dose of 0.3 Gm. of neoarsphenamine the patient felt feverish and had slight pain in the right upper abdominal quadrant. This was believed to be a Herxheimer reaction. She felt well the next day and the jaundice was noticeably decreasing.

A dose of 0.4 Gm. of neoarsphenamine was administered on April 24. About one hour and a half afterward the patient had a chill, fever, vomiting, abdominal cramps and increased tenderness in the right upper quadrant. The tenderness was still present two days later. This was believed to be a second Herxheimer reaction.

The jaundice and the tenderness in the right upper abdominal quadrant were much less marked on April 29, and 0.4 Gm. of neoarsphenamine was administered. The patient experienced no reaction.

No reaction followed 0.3 Gm. of arsphenamine on May 3.

A dose of 0.4 Gm. of neoarsphenamine was administered on May 7 because of difficulty encountered in introducing into the patient's small veins the 20 gage needle used in the gravity method of giving arsphenamine. There was no reaction. The skin and scleras showed no evidence of jaundice on that date, and there was a marked improvement of the papular secondary eruption. The macules had already faded.

The icterus index was 5, and urinalysis showed no bile on May 8. The patient departed from the clinic without permission on May 9, and she did not return.

Case 2.—J. J. J., a single Negro aged 19, was admitted to the clinic on May 21, 1935. He complained of a "sore" on his penis which had appeared about May 1. He said he had not previously had a genital lesion, a secondary cutaneous eruption or treatment for syphilis.

Physical examination showed him to be ambulatory and not acutely ill. He had a scar on his penis, a generalized maculopapular secondary cutaneous eruption and a pronounced icteric tinge of the skin and the conjunctivae, in spite of the fact that he was a Negro. There was a general adenopathy. The liver and spleen were not palpable.

Laboratory tests on May 21 showed 4 plus Kolmer and Kahn reactions and an icterus index of 90. Urinalysis gave negative results except for bile. A diagnosis of maculopapular secondary syphilis with benign hepatitis was made.

Treatment consisted of sixteen intramuscular doses of 2 cc. of a solution of bismuth potassium tartrate during the period from May 24 to July 3 and baths at Hot Springs six days per week.

No reaction was noted after any treatment. The maculopapular secondary cutaneous eruption had almost disappeared by June 3 and by June 8 had entirely disappeared. The patient did not feel ill. The icteric tinge had entirely disappeared by June 10. Kolmer and Kahn tests on June 1 and on July 3 gave 4 plus reactions, and determinations of the icterus index gave results of 8, 7 and 5, respectively, on these dates. On May 27 results of urinalysis were negative except for bile, and by June 10 they were completely negative.

The patient departed from the clinic without permission on July 6, and he did not return.

CASE 3.—C. A. R., a married man aged 56, was admitted to the clinic on June 28, 1934. He complained of a "sore" on his scrotum of about one month's duration. His skin had been yellow and itching since about June 15. He had received one dose of neoarsphenamine on June 22, after a 4 plus reaction to a Wassermann test of the blood, his skin being yellow at that time. He stated that he had not had a previous genital lesion or previous treatment for syphilis.

Physical examination showed him to be ambulatory, well nourished and not acutely ill. There was a small shallow ulcer on his scrotum. The scleras and the skin were very yellow. There were many excoriations on the trunk and upper extremities, due to the patient's scratching himself. The liver was felt 3 finger-breadths below the costal margin, and it was not tender. The spleen was not felt. His reactions to Kolmer and Kahn tests on June 28 were 4 plus. The icterus index was 100. On June 29 urinalysis gave negative results except for bile.

The patient's wife, aged 35, was admitted three weeks later, on July 19. She complained of a genital lesion first noticed by her about July 14. She stated that she had not previously had a genital lesion, treatment for syphilis or extramarital exposure. A dark field examination for Spirochaeta pallida of a small erosive ulcer of the left labium minus gave positive results on July 21. The patient's Kolmer and Kahn reactions were negative on July 19 and 2 plus on July 20. The diagnosis in her case was primary syphilis.

In view of this, the diagnosis in the case of the husband was primary syphilis with acute benign hepatitis. He was transferred to the Leo N. Levi Memorial Hospital on June 29 and received thirty-eight intramuscular doses of ⅓ grain (0.02 Gm.) of mercury benzoate during the period from July 3 to August 27. From July 24 to August 28 he received six doses of arsphenamine.

On July 1 urinalysis gave strongly positive results for bile. Kolmer and Kahn reactions of 4 plus were obtained on July 12, and the icterus index was 20. On July 13 the condition of the patient was improved; the icterus was not so marked; the feces were still pasty and clay colored, and the urine was still heavily loaded with bile. The patient felt better in general. By July 27 he was doing nicely, and his condition was improved. Urinalyses on August 9 and on August 17 gave negative results for bile. The Wassermann reaction on the spinal fluid was negative on August 18; 1 cell per centimeter was present. No globulin appeared on chemical examination. On August 24 the patient was doing nicely and felt a great deal better. The jaundice had cleared. On August 28 he was dismissed.

CASE 4.—W. D. U., a married man aged 22, was admitted to the clinic on April 22, 1935. He stated that he had had a genital "sore" in April, 1932, and that he had had six doses of neoarsphenamine and four intramuscular doses of mercury at that time without a previous dark field examination or Wassermann test. He had never had a Wassermann test before admission to this clinic. He

further stated that he had had a genital "sore" in January 1935 and said he had had no further treatment for syphilis after the six doses of neoarsphenamine in 1932.

Physical examination revealed him to be ambulatory and not acutely ill. There was no scar at the site of the genital lesion of 1932, but there was a scar at the site of the penile lesion of January 1935. There was a yellowness of the skin and conjunctivae, and there were mucous patches in the mouth, general adenopathy and a palpable tender liver. The spleen was not felt.

Laboratory tests showed Kolmer and Kahn reactions of 4 plus and an icterus index of 18. Urinalysis on April 23 gave negative results except for bile.

The diagnosis was secondary syphilis of the mucous membrane of the mouth with benign hepatitis of early syphilis, rather than relapsing secondary syphilis with a hepatorecurrence, for the reason that treatment for syphilis had been instituted in 1932 without a diagnosis based on a dark field examination or a Wassermann test and because of the unlikelihood of a relapse of the secondary type in the mucous membrane (mucous patches) after three years.

Treatment consisted of fourteen doses of neoarsphenamine (beginning with 0.01 Gm. and increasing to 0.3 Gm.) and fourteen intramuscular doses of 2 cc. of bismuth potassium tartrate during the period from April 23 to May 1, inclusive. The patient also received baths at Hot Springs six days per week.

There was no reaction after any of the first three small doses of neoarsphenamine. There was a slight reaction after a dose of 0.2 Gm. of neoarsphenamine on April 26. This was believed to be a Herxheimer reaction.

On May 8 Kolmer and Kahn reactions of 4 plus were obtained, and the icterus index was 10. Examination on May 10 and May 13 showed the jaundice to be decreasing, and on May 18 it had disappeared. On May 23 results of urinalysis were negative for bile.

The patient departed from the clinic without permission on May 31, and he did not return.

### COMMENT

It is believed that the first patient had benign hepatitis of early syphilis with two Herxheimer reactions of the hepatitis during treatment with neoarsphenamine and bismuth. The jaundice disappeared within nineteen days after treatment was instituted.

It is believed that the second patient had benign hepatitis of early syphilis. No Herxheimer reaction was noted objectively or subjectively during treatment. This patient was treated with bismuth but not with arsphenamine. Frequent determinations of the icterus index might have shown a Herxheimer reaction, as in the case of Elliott and Todd.[5] Jaundice disappeared within seventeen days after treatment was instituted.

It is believed that the third patient had benign hepatitis of early syphilis. There was no Herxheimer reaction during treatment. The patient had preliminary intramuscular injections of mercury benzoate for three weeks, and the jaundice and the general condition of the patient improved during this time. The jaundice had entirely disappeared within forty days after treatment with mercury was instituted and within sixteen days after treatment with arsphenamine was begun.

It is believed that the fourth patient probably had benign hepatitis of early syphilis, with a Herxheimer reaction of the hepatitis during treatment with neoarsphenamine and a bismuth preparation. Jaundice disappeared within twenty-five days after treatment was instituted.

## SUMMARY

Three undoubted cases of benign hepatitis of early syphilis and 1 probable one (case 4) are presented. Two patients, who were treated with neoarsphenamine and bismuth, had Herxheimer reactions. The patient treated with bismuth alone and the patient who received preliminary intramuscular injections of mercury benzoate before treatment with arsphenamine showed no clinically recognizable Herxheimer reactions.

It is believed that there is no danger of trouble due to a severe Herxheimer reaction if an arsphenamine preparation is used from the outset in the treatment of patients with benign hepatitis of early syphilis, provided treatment is instituted with very small doses of the arsphenamine preparation and the patient is carefully watched.

# EFFECT OF AGE ON CONSUMPTION OF OXYGEN AND COMPOSITION OF THE SKIN OF THE ALBINO RAT

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CINCINNATI

Andrews [1] stated that age and sex are both predisposing factors in the cause of cutaneous diseases and that there are certain conditions of the skin that are found almost exclusively in definite regions of the body. Schmidt [2] concluded that the type of biologic and cutaneous reaction is conditioned by the individual constitution and the degree of instability of the autonomic nervous system, and that the weather is an important environmental factor in precipitating cutaneous symptoms. Schmidt [3] had previously shown by means of staining reactions and by intracutaneous injections of methylene blue that the requirement for oxygen varies in different parts of the surface of the body. Kadisch [4] had shown a relation between the localization of infections, the temperature and the supply of oxygen to the skin.

Oxidation, either aerobic (by means of oxygen directly) or anaerobic (by means of easily reducible substances) is essential for the production in the living cell of the energy by which it carries out its growth and other physiologic processes. The respiration of the skin is therefore probably a more accurate measure of its vitality than any other of its functions. If measures of the respiration of the skin were made in different areas of the body, at varying ages and in normal and pathologic states, then its physiologic status could be determined and understanding of the fundamental processes involved in cutaneous diseases advanced.

Preliminary to more extended studies on the physiology and biochemistry of the skin it was necessary to determine the effect of certain

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1. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1932, pp. 17-18 and 70.

2. Schmidt, F. R.: Skin Diseases and Weather, Arch. Dermat. & Syph. **32**: 781-786 (Nov.) 1935.

3. Schmidt, F. R.: Blood and Oxygen Supply of the Skin, Arch. Dermat. & Syph. **32**:576-579 (Oct.) 1935.

4. Kadisch, E.: Arch. f. Dermat. u. Syph. **168**:438-476, 1933.

factors on the absorption of oxygen. The experiments presented show the effect of the age of normal albino rats on the absorption of oxygen in vitro and on the composition of the skin.

## PROCEDURE

The absorption of oxygen was determined on the surviving skin of albino rats by the method of Warburg.[5] Total lipids were determined by the method of Bloor.[6] From part of the total lipids extracted the phospholipids were isolated and the phosphorus determined by the method of Fiske and Subbarow.[7] The total dry matter was determined by heating a thinly sliced portion of the skin at 100 C. for several hours. The rats were secured from the Wistar Institute at weaning time. They were maintained on a diet of casein, potato starch, freshly ground whole wheat, cod liver oil, butter fat and F. R. L. salt mixture.[8]

*Consumption of Oxygen and Composition of Skin of Rats*

| Animal Number | Age in Days | Oxygen Consumption per Mg. Fat-Free Dry Matter | Water Content of Fresh Weight, % | Water-Free Dry Matter of Fresh Weight, % | Fat-Free Dry Matter of Fresh Weight, % | Total Lipid of Fresh Weight, % | Phospholipid (P × 25.06) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Of Fresh Weight, % | Of Total Lipid, % | Of Water-Free Dry Matter, % | Of Fat-Free Dry Matter, % |
| Suckling | 10 | 4.90 | 67.80 | 32.20 | 11.50 | 20.66 | 1.12 | 5.41 | 3.47 | 9.70 |
| 24 C | 36 | 3.60 | 68.53 | 31.47 | 20.86 | 10.60 | 0.807 | 7.61 | 2.56 | 3.86 |
| 5 R | 79 | 1.75 | 59.10 | 40.90 | 25.60 | 15.30 | 0.475 | 1.85 | 1.16 | 3.10 |
| 6 A | 105 | 1.49 | 59.73 | 40.27 | 27.84 | 12.53 | 0.546 | 4.39 | 1.35 | 1.96 |
| A | 180 | 1.23 | 62.62 | 37.38 | 29.50 | 7.85 | 0.329 | 4.20 | 0.89 | 1.11 |
| O | 210 | 0.50 | 63.47 | 36.53 | 32.30 | 11.17 | 0.494 | 11.90 | 1.35 | 1.52 |

## COMMENT

Preliminary experiments on the oxygen consumption of the skin indicated that there was a marked difference between the amount of oxygen absorbed by the skin of very young and very old rats. The oxygen consumption (expressed in cubic millimeters of oxygen per hour at 0 C. and 760 mm. pressure) of rats from 1 to 5 weeks old varied from about 3 to 5 per milligram of fat-free dry matter. The table presents the oxygen consumption and the composition of the skin of rats varying in age from 10 days to 7 months.

The oxygen consumption fell regularly from 4.9 per milligram of fat-free dry matter at the age of 10 days to 0.5 at 210 days. The preliminary series, in which no analyses were made, however, indicated

5. Warburg, O.: Biochem. Ztschr. **142**:317-333, 1923.
6. Bloor, W. R.: J. Biol. Chem. **82**:273-286, 1929.
7. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375-400, 1925.
8. Hawk, P. B., and Bergeim, Olaf: Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 693.

that the oxygen consumption of the skin of mature animals (not carefully selected for age, parentage, diet, weight, etc.) may vary from as low as 0.25 to as much as 1 per milligram of fat-free dry matter. In the further series of more uniform animals reported in table 1, it will be seen that the oxygen consumption falls rapidly until the subject approaches the age of 50 days, after which it may vary within certain limits but remains far below that in young, rapidly growing animals. The bodily metabolism of human beings [9] as well as of albino rats declines with age. Davis and Hastings [10] have shown that the decline continues until about the fourth month.

The data presented for oxygen consumption compare favorably with the observations of Loebel,[11] who found values for the skin of new-born white mice as high as 5.8 per milligram of water-free dry matter and for the skin of one new-born white rat a value of 3.5. The value for the skin of a mature rat is much lower than that found by Klopstock [12] for fresh human skin (adult). He found an average oxygen consumption of 2.1 per milligram of water-free dry matter, with values ranging from 1.2 to 5.1. Hawkins [13] stated that the metabolism of tissue isolated from the liver of rats is approximately the same for animals of different ages, except in the very young. Meyer, McTiernan and Aub [14] found that in mice age has little effect on the metabolism of isolated tissues. The present investigation confirms that general conclusion, in that in very young rats the oxygen consumption may be about as high as 5 per milligram of fat-free dry matter, the value dropping at from 4 to 6 weeks to a relatively constant value of about 0.5. From this age on, however, the value may vary in nonuniform animals (i. e., animals differing in parentage, size and diet) from 0.25 to as much as 1.

The water-free dry matter, which includes lipids, does not show quite such regular change with age as does the fat-free dry matter. The water-free dry matter will vary with the amount and type of feeding. The water content of the skin shows an appreciable fall with age—from 67.8 per cent in the skin of young animals to an average value of about 60 per cent for animals from 79 to 210 days old. Simultaneously, the percentage of fat-free dry matter in the fresh skin increases from 11.5 per cent at the age of 10 days to 32.3 per cent at 210 days.

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9. Benedict, F. G.: Basal Metabolism: II. An Index of Vital Activity, News Service Bulletin 11, Carnegie Institute of Washington, 1931, p. 99.

10. Davis, J. E., and Hastings, A. B.: Am. J. Physiol. **109**:683-687, 1934.

11. Loebel, R. O.: Biochem. Ztschr. **161**:219-239, 1925.

12. Klopstock, E.: Biochem. Ztschr. **175**:202-215, 1926.

13. Hawkins, J. A.: J. Gen. Physiol. **11**:645-647, 1928.

14. Meyer, O. O.; McTiernan, C., and Aub, J. C.: J. Clin. Investigation **12**: 723-735, 1933.

Apparently the dry matter of the skin increases to a greater extent than the dry matter of other organs. Lowrey [15] determined the dry matter (including hair, ears, nails and lipids) of the whole skin and of some of the internal organs of rats of varying ages. He found that the skin of rats at birth contain 12.3 per cent of dry matter. This rapidly increases to 41.1 per cent at the age of 20 days and then more slowly to 45.5 per cent at 12 months. Although the analyses reported here do not show such a high content of dry matter (having been made on the shaved skin and not including hair and nails), it is evident that the figures are parallel and indicate a much higher content of dry matter than for most of the internal organs. Taking Lowrey's figures for comparison: For the liver, dry matter was 19.4 per cent at birth and rose gradually to 26 per cent at 12 months; for the musculature, dry matter was 10.7 per cent at birth and rose gradually to 23.8 per cent at 12 months. The striking increase in dry matter of the skin which Lowrey found in the twenty days after birth was probably caused in part by the increase in hair, since rats are born hairless and show appreciable growth of hair in the two weeks after birth. Regardless of the absolute amounts, it is shown by the analyses reported here that the dry matter almost doubles between the ages of 10 and 36 days; whereas by the data of Lowrey the dry matter in the musculature just a little more than doubles in twelve months and the hepatic dry matter increases in twelve months only about one-third.

It has long been known that the water content of tissues decreases with age. Donaldson [16] showed that the water content of the brain and spinal cord of rats is linked with age and is not readily modified by nutritive conditions. Bürger and Schlomka [17] analyzed the skin of fresh cadavers and found the water content to decrease up to 70 years of age. They expressed the belief that the loss of water is a very basic phenomenon of the aging of tissues. On the basis of water content, then, one might say that the skin ages faster than other organs, since the dry matter increases to a greater extent there than in other organs, with simultaneous and proportional loss of water.

On the other hand, the percentage of phospholipids in the skin declines with age. In very young animals it is 1.12 per cent of the fresh weight, or 3.47 per cent of the water-free dry matter. In animals of 79 days it has fallen to an average level of about 0.5 per cent of the fresh weight and about 1 per cent of the water-free dry matter. Since

15. Lowrey, L. G.: Anat. Rec. **7**:143-168, 1913.

16. Donaldson, H. H.: J. Comp. Neurol. & Psychol. **20**:119-144, 1910; **27**:77-115, 1916.

17. Bürger, M., and Schlomka, G.: Ztschr. f. d. ges. exper. Med. **58**:710-724, 1928.

the water-free and fat-free dry matter increases markedly with age, this decline of phospholipids to a relatively constant level may be interpreted in several ways, depending on which theory of the function of the phospholipids is accepted. Whether the theory that they are intermediate stages in fat metabolism or the hypothesis that they are structural elements of the living matter is accepted, it is remarkable that there appears to be a conservation of the phospholipids. This seems likely, in view of the relatively moderate decline in phospholipids as compared with the increase of dry matter.

Since the work of Mayer and Schaeffer [18] the weight of evidence seems to favor their point of view. They detected no significant effect of fasting, overfeeding or type of diet on the amount of phospholipid in the various tissues. The remarkable constancy and the universal distribution of the phospholipids led them to conclude that the phospholipid has some more general and more fundamental function than that of a fuel. They suggested that they act as carriers of oxygen and as part of the organic basis of living matter.

## CONCLUSIONS

The consumption of oxygen, and the water, the phospholipid and the total lipid content of the skin of normal albino rats decline with age to a relatively constant value. The amount of total lipids, however, varies irregularly.

The fat-free dry matter almost doubles between the ages of 10 and 36 days, after which it continues to increase more slowly to about the age of 210 days. Because of the variations in the total lipids, oxygen consumption should be calculated on the basis of fat-free dry matter.

Dr. Albert P. Mathews gave criticism and advice in this study.

18. Mayer, A., and Schaeffer, G.: J. de physiol. et de path. gén. **15**:733-788. 1913; **16**:325-336 and 344-359, 1914.

# Clinical Notes

## AN INSECTICIDE (FLIT) AS A CAUSE OF DERMATITIS

### Report of a Case of Eighteen Months' Duration in Which the Husband Was the Carrier

HERMAN GOODMAN, M.D., NEW YORK

Flit is a popular brand of insecticide. The opportunity for contact dermatitis is frequent, yet there is a paucity of reports on any ill effect.

I am able to report a case of such irritation, with the clinical and experimental evidence of the source of dermatitis. This persisted for eighteen months because the true nature of the affliction was not determined.

#### REPORT OF CASE

Mrs. F. G., a housewife aged 37, American born, moved to new quarters in April 1935 and immediately began to suffer from itching. Failing to secure relief through treatments prescribed by physicians, she employed various types of home medication. Prescriptions used by friends and relatives were accepted gratefully and discarded.

During November 1936 the patient came under my observation and showed a conglomeration of eruptive lesions. The lesions on the breasts, buttocks and protuberant portions of the body in general were individual papules interspersed with scratch marks. The axillae, the groins, the sides of the neck, the flexures of the elbows, the popliteal spaces and parts of the lower portion of the legs were most affected. Some of the involved areas were the size of the palm; others were the size of a thumb-nail. The clinical picture seemed to indicate the sleeping position as the best explanation for the sites of the lesions.

The patient recalled that when she moved to her new quarters in April 1935 she had used a brand of insecticide (Flit) for the first time and had not changed it since residing in her new home.

On her next visit she brought a small container, and its contents were used to test the patient for sensitivity. A drop applied to the unbroken skin and another drop applied on a scratch led to two violent local reactions. At the expiration of twenty-four hours a little Flit was permitted to run down over an area of skin which showed diminishing intensity of eruption. The next day the patient presented a general flare-up in all the areas of the body which had been inflamed during the preceding eighteen months.

It is curious that the patient had never noted any regular recurrence of the symptoms. Treatment of all kinds seemed to help for a short time. Absence from the city also gave relief for a short time. Owing to duties in the care of husband and children, the patient was never away from her own home for more than a week.

The interval between sprayings for the house in general and for the beds in particular was never less than seven nor more than eight days. It seemed to be a duty the maid enjoyed, and she must have done the spraying thoroughly. The

patient was directed to sleep on a newly purchased cot. After a long period of quiescence, she had a recurrence of the itching and of the eruptive lesions. She stated that she had not been exposed to Flit in any way. Questions elicited the information that her husband, who had slept on the bed which had been sprayed for almost two years, acted as a carrier of sufficient Flit to reactivate the patient's lesions.

On another occasion after a lull, the patient acted as nurse for her child who had influenza. The child slept in the bed formerly occupied by the mother. During the short periods required to lift the child for such purposes as changing the bed linen, the mother was again exposed to an amount of Flit sufficient to give rise to a pruritic eruption, although for several months Flit had not been used in the home.

The patient recognized that relief from the eruption depended on ridding her home of everything which had been in contact with the insecticide. The beds, mattresses and springs were given to relatives. Blankets, linens and pillows were sent to cleaners. Rugs were aired. Carpets were torn up. The patient was finally in surroundings free from the insecticide, and the cutaneous eruption no longer troubled her.

In the early part of 1937 she had a recurrence of the eruption and pruritus. Her faith in physicians was completely shattered. A little detective work disclosed these facts: The husband had spent a week at his mother's house. During that week he had occupied the bed which had been sent from his home. He had bathed, changed his linen and removed any apparent possibility of carrying whatever Flit was left in the bed; yet his wife showed her clinical upset the day after his return.

There seems to be no doubt that Flit was the cause of this woman's eruption. I have made no attempt to learn which component of Flit was responsible.

# Minor Notes

## PIGMENTED SPOTS OF THE MUCOUS SURFACE OF THE LIPS

WILLIAM ALLEN PUSEY, M.D., CHICAGO

For many years I have observed pigmented spots on the inner surface of the lips which have appeared spontaneously and without symptoms. The condition is evidently not rare; I have seen perhaps a dozen cases of it. A typical picture of the condition was present in the first case I observed. The patient was a woman about 40 who has occasionally consulted me until the present time for other conditions and whom I had seen for other troubles for several years before I observed the spots. The lesions, five or six in number, appeared while she was under my observation and developed in about six months. In her case they disappeared spontaneously in the course of several years.

The lesions to which I refer consist simply of smooth pigmented spots without elevation, infiltration or changes in the surface of the skin. They are dark brown, almost black, and irregular or roughly circular and measure from 2 or 3 to 8 or 10 mm. in diameter. They are not associated with abnormal sensation and usually cause the patient to seek advice because of curiosity or of fear that the lesions may be malignant. The lesions vary in number from two or three to perhaps a dozen and are irregularly symmetrical. In most cases they are limited to the inner surface of the lips; they appear more often on the lower lip than on the upper, and sometimes they are confined to the lower lip. In some cases there have been lesions on the buccal mucosa. The spots have not been associated with pigmentary anomalies of the skin or disturbances of the general health.

I have not examined any of them histologically, but I have no doubt that a biopsy would show simply normal pigment in the usual location. The lesions have not been suggestive of malignant disease. So far as I know, in none of the cases I have observed has malignant degeneration developed anywhere in the body later, and in my opinion the lesions are not in any way ominous. They are, I believe, a dyschromia without significance, a clinical curiosity.

I have made no effort to remove the lesions, although I think that their removal could easily be accomplished by freezing them for ten seconds with solid carbon dioxide.

## INEFFICACY OF SIROIL AS A REMEDY FOR PSORIASIS

J. LAMAR CALLAWAY, M.D., DURHAM, N. C.

Siroil, a patent medicine which has enjoyed a rather widespread popularity among laymen as a result of extensive advertising in various magazines and newspapers, has been subjected to a careful study both as to its chemical composition and as to its therapeutic value.

From the Department of Dermatology and Syphilology, School of Medicine, University of Pennsylvania, John H. Stokes, Director.

During the winter of 1936 twenty-six patients with psoriasis were treated with siroil. Of these, fourteen had been previously unsuccessfully treated and twelve had received no treatment. Nine patients were treated with siroil purchased on the open market, and seventeen were treated with a "synthetic siroil." [1] The "synthetic siroil" was prepared according to the analysis published by the Bureau of Investigation of the American Medical Association [2] and our own analysis, the results of which were almost identical with those reported by the Bureau. All the samples analyzed were purchased on the open market, and minor differences observed in chemical composition may be explained by inconsistency in manufacturing.

To control the observations of the effect of siroil, the patients were given a plain oil mixture (the same mixture as that which forms the base of siroil) and instructed to apply it to one half of the body at the same time siroil was applied to the other half. Printed instructions identical with those on bottles containing siroil were given to the patient for the use of the mixture.

Of the nine patients treated with siroil, one was temporarily improved and two had a dermatitis venenata. Of the seventeen patients treated with the "synthetic siroil," one was improved and three had a dermatitis venenata. No patient was permanently improved. The plain oil mixture seemed to be as beneficial as the siroil or the "synthetic siroil." About the only thing which any of the preparations seemed to do was remove some of the superficial scales.

My experience indicated that siroil is not an efficacious remedy for the treatment of psoriasis. This is in agreement with the experience of the Bureau of Investigation of the American Medical Association, which found that "Siroil occasionally helps, occasionally harms and frequently does neither one nor the other," and with that of Becker,[3] who stated that "siroil has no particular virtues. The shock of having to pay $5 for a bottle of the medicament may have something to do with the miraculous relief which the patients claim to have had."

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1. Analyses of siroil and the preparation of the synthetic siroil were performed by the Dermatological Research Laboratories, Dr. George W. Raiziss, Director.

2. Siroil: A Patent Medicine for Psoriasis, report of the Bureau of Investigation, J. A. M. A. **105**:299 (July 27) 1935.

3. Becker, S. W.: Personal communication to the author.

# Editorial

## SOCIETY TRANSACTIONS

Considerable improvement has been made recently in the transactions of dermatologic societies published in the ARCHIVES. Mimeographed sheets calling attention to the style of writing required by publications of the American Medical Association have been sent to all members of the societies issuing transactions, and the response to these suggestions has been gratifying. Several societies have profited by appointing committees to edit their transactions before submitting them for publication. Societies which have experienced reporters usually furnish the best manuscripts.

The space allotted to society transactions in the ARCHIVES in comparison with that in foreign dermatologic journals is extremely liberal. Certain cases presented before dermatologic societies are of great interest to those present though not of sufficient value for publication. Reports of these are omitted and only the titles published. The same disposition is made of cases which are inadequately or carelessly reported.

It has not been the custom to include illustrations in society transactions. This may be done, however, when a good photograph is offered and the expense of reproduction is borne by the author or by the society he represents.

It is urged that all who contribute to the transactions familiarize themselves with the form in which reports of cases are published in the ARCHIVES. It is useful, too, to retain copies of the reports submitted and to note the editorial changes appearing in the printed version. Greater care in the preparation of reports would lessen the task of the manuscript editors—not to mention that of the editor.

H. F.

# News and Comment

## SOCIÉTÉ FRANÇAISE DE DERMATOLOGIE ET DE SYPHILIGRAPHIE

The following regulations have been announced for the awarding of an anonymous biannual prize of 5,000 francs through the Société française de dermatologie et de syphiligraphie:

1. The prize will be awarded every two years for the best essay (printed or in manuscript) on a subject relating to cutaneous or venereal diseases, provided that the essay represents a true scientific advance. Every alternate time the prize will be competitive, the subject being given by the executive committee.

2. The prize may be divided among several competitors.

3. Competitors may be either French or foreign writers, but the manuscripts must be written in or translated into French.

4. Competitive essays include those which have been printed in the two preceding years or unpublished manuscripts which must be published during the year following the award of the prize.

5. The jury is authorized to award the prize for an essay which has been published without having been presented at a medical society.

6. The competitive essays must be sent to the secretary-general of the society postpaid before November 30 and announced at the general assembly which follows.

7. Essays will belong to their authors, but eight printed copies must be presented to the society, one copy being reserved for the founder of the prize. An abstract of the essay will appear in the Bulletin immediately after the prize is awarded.

8. The committee which awards the prize will be named by the executive committee at a meeting in December, after the receipt of the essays. It will consist of nine members, including five members of the executive committee and four persons chosen by the society from a list of eight names presented by the executive committee.

9. The present regulations may be revised when requested by a petition signed by fifteen members of the society.

The prize will be awarded for the first time in 1939 and will be competitive.

The executive committee has chosen the following subject: "The Process of Sensitization and Immunization in the Epidermomycoses (Dermatomycoses)."

Essays should be sent to the secretary-general, Dr. Pierre Fernet, 11 Rue de Sontay, Paris, 16e, before Nov. 30, 1938. Award of the prize will be announced at the general assembly in May 1939.

## PROGRAM NOTICE, SAN FRANCISCO MEETING OF AMERICAN MEDICAL ASSOCIATION, JUNE 13-17, 1938

Applicants for places on the program of the Section on Dermatology and Syphilology at the Annual Session of the American Medical Association in San Francisco, June 13-17, 1938, are requested to submit titles and provisional abstracts of their proposed papers to the secretary of the section, Dr. Bedford Shelmire, Medical Arts Building, Dallas, Texas.

Applicants need not be members of the section but must be Fellows of the Association, graduates in medicine not in private practice or invited guests.

## INTERNATIONAL LEPROSY CONFERENCE

Arrangements are being made to open the fourth International Leprosy Conference in Cairo on March 21, 1938. This conference is being organized by the International Leprosy Association and will be the first international conference to be arranged by that group since its organization in 1931. Three previous conferences of a similar nature have been held: in Berlin in 1897, in Bergen, Norway, in 1909 and in Strasbourg, France, in 1923.

The Egyptian government is inviting all countries concerned to send official delegates. In addition to these, physicians and others interested in the subject are invited to be present. Full information can be obtained from the secretary of the International Leprosy Association, Dr. Ernest Muir, 131 Baker Street, London, W.I.

## COMMITTEE ON VENEREAL DISEASE ACTS ON REPORT

At the meeting of the American Dermatological Association, from June 9 to 11, a committee was appointed to cooperate with the Public Health Service in relation to the control of venereal diseases. This committee consists of Drs. Harold N. Cole, N. N. Epstein, H. H. Hazen, Paul A. O'Leary and Earl D. Osborne. It has approved the report of an advisory committee to the United States Public Health Service (Recommendations for a Venereal-Disease Control Program in State and Local Health Departments, Ven. Dis. Inform. **17**:1-16 [Jan.] 1936).

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## CORRECTION

In the article by Drs. William T. Corlett and Paul E. Bechet, "Section on Dermatology and Syphilology of the American Medical Association: Its Foundation and Early Years," in the July issue (ARCH. DERMAT. & SYPH. **36**:45, 1937), the name Revogli is misspelled. It should read Ravogli.

# Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

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THE RESPONSE OF THE QUANTITATIVELY TITERED WASSERMANN TEST IN EARLY SYPHILIS TO TREATMENT WITH FIVE DIFFERENT ARSENICAL DRUGS. J. E. MOORE, S. M. HARDY, H. M. ROBINSON and H. EAGLE, Am. J. Syph., Gonor. & Ven. Dis. **20**:503 (Sept.) 1936.

Weekly quantitative Wassermann tests were performed during the first course (eight injections) on seventy-eight patients treated with arsphenamine, on seventy-four treated with neoarsphenamine, on thirty-five treated with silver arsphenamine, on twenty-one treated with bismarsen and on eighty-one treated with mapharsen. The average response to the quantitatively titered Wassermann test in early syphilis was approximately the same with four of the five drugs studied, i. e., arsphenamine, silver arsphenamine, bismarsen and mapharsen; it was slightly less satisfactory with neoarsphenamine. Since the five drugs are not of equal value with respect to other important results of treatment, the rate of reversal of the Wassermann reaction in early syphilis after treatment with a given drug can be regarded as only a relatively unimportant factor in the final evaluation of that drug.

The authors enumerate the important criteria for the evaluation of an antisyphilitic drug.

THE VALUE OF THE KLINE EXCLUSION TEST IN THE SERODIAGNOSIS OF SYPHILIS. C. R. REIN, Am. J. Syph., Gonor. & Ven. Dis. **20**:515 (Sept.) 1936.

In the recent evaluation plan for the serodiagnosis of syphilis devised by the United States Public Health Service in cooperation with the American Society of Clinical Pathologists, the Kline exclusion test with heated serum was the most sensitive of all the tests in group A (less than 1 per cent false positive reactions in 468 presumably nonsyphilitic persons were obtained). By means of this test more persons with primary and latent syphilis were detected than by any other test in group A.

As secondary considerations, the low cost of materials and the rapidity and ease of performance of the slide tests deserve the highest regard.

REUTER, Milwaukee.

HERPES AND CHICKEN-POX IN THE SAME PATIENT. R. H. M. HARDISTY, Canad. M. A. J. **35**:310 (Sept. 1936.

A man aged 73 had a typical zosteriform eruption on the right side of the face. Seven days from the time of his initial symptoms an eruption typical of varicella appeared over the trunk. Hardisty is of the opinion that the two diseases are caused by the same etiologic agent.

CARCINOMA ORIGINATING IN SEBACEOUS CYSTS. D. C. COLLINS, Canad. M. A. J. **35**:370 (Oct.) 1936.

From a consideration of the literature and on the basis of his own experience, Collins states that all sebaceous cysts should be considered as precancerous lesions and should be closely observed if the patient does not consent to their surgical removal. In the routine examination of approximately 9,000 pathologic specimens, Collins observed two instances of carcinoma and one instance of precancerous changes (0.033 per cent) in sebaceous cysts. In the first case, the lesion was present on the anterior aspect of the abdominal wall; the histologic section showed

a grade 2 epidermoid carcinoma. In the second case there was a wen on the right side of the face, examination of which revealed a grade 3 epidermoid carcinoma. Beginning malignant changes were noted in a histologic specimen removed from the palm in a third case.

COMMON TUMORS OF THE EYELIDS. C. S. O'BRIEN and A. E. BRALEY, J. A. M. A. **107**:933 (Sept. 19) 1936.

O'Brien and Braley state that the differentiation by clinical means alone of lesions of the eyelids is sometimes difficult or impossible. Histologic as well as clinical study of 100 consecutive tumors of the lids showed the incidence to be as follows: papilloma, 34; nevus, 17; sebaceous cyst, 13; basal cell epithelioma, 13; fibroma, 5; sudoriferous cyst, 4; hemangioma, 4; epidermoid carcinoma, 2; dermoid cyst, 2; molluscum contagiosum, 2; sweat gland adenoma, 1; xanthelasma, 1; granuloma, 1, and melanoma, 1. In the discussion following the reading of this paper, Reese gave comparative statistics on another group of 100 consecutive tumors removed from eyelids. His study revealed the incidence to be as follows: basal cell epithelioma, 21; papilloma, 18; hemangioma, 11; nevus, 8; sebaceous cyst, 6; dermoid cyst, 5; sudoriferous cyst, 5; squamous cell carcinoma, 4; granuloma, 4; basosquamous cell carcinoma, 3; adenoma, 3; neurofibroma, 3; melanoma, 2; xanthoma, 2; lymphangioma, 1; lymphosarcoma, 1; teratoid tumor, 1; foreign body reaction, 1; traumatic inclusion cyst, 1.

TREATMENT OF DEMENTIA PARALYTICA. F. G. EBAUGH and J. R. EWALT, J. A. M. A. **107**:1031 (Sept. 26) 1936.

Sixty patients suffering from the adult form of dementia paralytica were divided equally into two groups for treatment. One group were treated with artificial hyperpyrexia and tryparsamide, while the second group were given malaria therapy. The patients in both groups later received injections of tryparsamide, and some also were given a bismuth preparation. For the thirty patients treated by hyperpyrexia, the average number of hours of fever (105 to 106 F.) was forty-four and five-tenths. The average number of treatments was 10.4, given at intervals of from four to seven days. Doses of 2 Gm. of tryparsamide were administered during the first or second hour of elevated temperature. In the malaria therapy, a tertian strain of Plasmodium was used for inoculation. From 1 to 2 cc. of citrated blood from patients with malaria was injected either intravenously or intramuscularly. The average number of elevations of temperature was 9.9, while the average number of chills was 8.2. Six injections of neoarsphenamine were followed by therapy with tryparsamide. All of this treatment was administered during the year from February 1935 to February 1936, and the results were analyzed in April 1936. It was found that in 70 per cent of the patients treated by hyperpyrexia a complete clinical arrest or improvement had resulted. In the group treated with malaria 63.3 per cent were likewise helped. Serologic studies of the cerebrospinal fluid revealed a complete reversal of reaction or a favorable change in 33.3 per cent of patients in the first group, as compared with a similar change in 39.9 per cent of the patients treated with malaria.

SPOROTRICHOSIS. G. M. LOEWE, J. A. M. A. **107**:1040 (Sept. 26) 1936.

A woman aged 30 in December 1931, after suffering from a severe rhinitis, had a pea-sized nodule in the region of the anterior cervical lymph nodes. In two weeks the nodule was fluctuant and was incised. Cultures and inoculation of animals showed no fungi. A tumor the size of a hen's egg remained in the tissues, and from this a sinus tract led to the surface of the skin. Several months later the swelling suddenly increased in size and chills and fever developed. This condition continued for two months. A biopsy revealed a "chronic granuloma probably of mycotic origin." Treatment included administration of potassium

iodide, nucleotide and gold sodium thiosulfate, roentgen and ultraviolet irradiation, and surgical drainage. In February 1933 bacteriologic studies isolated a sporothrix and a beta hemolytic streptococcus. On the basis of this information, Loewe made a diagnosis of sporotrichosis. He used inhalations of ethyl iodide, and administration of autogenous sporothrix vaccine, streptococcus vaccine and streptallergin, and clinical improvement resulted. In April 1934 local treatment consisting of irrigations with a 1 : 30,000 solution and of applications of a 1 : 1,500 ointment of phenylmercuric nitrate was used twice daily in conjunction with irrigation of the sinuses once daily with a dilute solution of sodium hypochlorite. By June 1934, cure was complete.

[The difficulty in obtaining a cultural growth of Sporotrichum Schenckii is unusual. It is also odd that this strain resisted iodides. Another interesting feature is the localization of the infection with apparently no tendency to spreading to other parts. The location, localization, lack of response to therapy and difficulty of making a cultural diagnosis would speak more in favor of actinomycosis. No mention is made of a search of fresh preparations of pus for fungi. Details regarding the nature of the cultural growth are also lacking. It is possible that agglutination, complement fixation or intracutaneous tests might have aided in proving the diagnosis.—Abstracter.]

MYELOGENOUS LEUKEMIA WITH CUTANEOUS INVOLVEMENT. S. M. GOLDHAMER and B. F. BARNEY, J. A. M. A. **107**:1041 (Sept. 26) 1936.

A man aged 41 had noticed increasing weakness, palpitation and dyspnea on exertion during the seven months prior to his first visit. Examination revealed a large spleen, an increase in the size of liver, bleeding hemorrhoids, generalized lymphadenopathy and cutaneous lesions. The cutaneous lesions consisted of six nodules the size of a half cherry which were discrete and attached to the overlying skin. They were firm and not tender. The overlying skin was dully erythematous. The histologic section revealed ". . . an infiltration of myeloid cells in nodular formation, located deep in the corium overlying the adipose tissue. The papillae showed no definite infiltration, nor did the more superficial layers of the corium. The epithelium appeared atrophic, and there was a decrease in the sebaceous and suderiferous glands, apparently from pressure. The infiltrate for the most part was sharply demarcated and surrounded by a fibrous capsule. Within the blood vessels was seen the blood picture of myelogenous leukemia.

"The cells of the infiltrate were large, pale-staining mononuclear cells, some of which contained granules, and others were agranular. Interspersed between these were stroma or fibrous tissue cells. Schultze's stain for oxidase granules was positive."

The blood contained 2,630,000 red cells and 122,800 white cells per cubic millimeter. The differential count was compatible with a diagnosis of myelogenous leukemia in over one hundred observations. At autopsy, leukemic infiltrations were noted in most of the organs. In this case, as in the sixteen previously recorded cases of similar conditions, the cutaneous manifestations appeared late in the course of the disease. Goldhamer and Barney thus postulate that when cutaneous involvement occurs the expectancy of life may be only a few weeks.

USE OF THE DERMAL PARASITICIDES. F. WISE and J. WOLF, J. A. M. A. **107**:1126 (Oct. 3) 1936.

The first requisite for the successful treatment of the superficial fungous diseases is an accurate diagnosis, which may at times be suggested by the clinical appearance of the eruption. In some instances, the identity of the causal organism influences the type of therapy prescribed. Wise and Wolf list the most important parasiticides, give the indications for their use and provide prescriptions in which they are incorporated. The treatment of diseases caused by animal parasites is also briefly considered.

LEWIS, New York.

SCLEREDEMA APPEARING DURING ACUTE NEPHRITIS: BLOOD STUDIES. H. JANET, R. GAUBE and J. GAUTIER, Bull. Soc. de pédiat. de Paris **33**:206 (March) 1935.

A girl 11 years old had otitis media and mastoiditis following an acute infection of the upper respiratory tract. A short time afterward she had acute hemorrhagic nephritis accompanied by scleredema of the skin, which did not involve the fingers and toes. She showed progressive improvement and recovered. It is pointed out that scleredema is a relatively benign involvement of the skin, consisting of swelling and infiltration of the collagen network; there is no inflammatory lesion or alteration of the papillae, and the elastic tissue is intact. Scleroderma is a much more serious condition, which begins insidiously as scleredema and then spreads gradually over the entire body. The body becomes hidebound when the stage of scleroderma with atrophy of the true skin occurs. The outlook in a case of scleroderma is grave, and death usually supervenes within a few years. The girl presented hyperlipemia, with an increase of the lipoids and a diminution of the proteins in the serum, and the albumin-globulin ratio was lowered. Thyroid extract was administered for a time but had no appreciable effect on the scleredema, which slowly disappeared spontaneously.

CUTANEOUS TUBERCULOUS LESION OF THE LOWER EXTREMITY; FISTULOUS INGUINAL ADENOPATHY; PROBABLE PRIMARY INFECTION. M. ARMAND-DELILLE and R. LESOBRE, Bull. Soc. de pédiat. de Paris **33**:215 (March) 1935.

A boy 3 years old presented an indolent ulcer over the right external malleolus and right inguinal adenitis with a fistulous tract, which had persisted after an incision made six months previously. The tuberculin reaction was positive; tubercle bacilli were grown from the discharge which exuded from the fistula, and biopsy of material from the edge of the ulcer revealed a typical tuberculous granulomatous structure with some surrounding sclerosis. There was no evidence of any other tuberculous foci in the body, including the lungs, and it is believed that this was a case of primary tuberculosis of the skin, a condition which is rare. A report of another case, which was probably one of the same condition, is appended, that of a boy 7 years old who had a lesion about 1 cm. in diameter on the left buttock and an enlarged left inguinal gland, from which pus was aspirated that showed tubercle bacilli in stained smears.

BENJAMIN, Montreal, Canada. [AM. J. DIS. CHILD.]

CHEILITIS GLANDULARIS OF VOLKMANN (DEEP SUPPURATING TYPE WITH EPITHELIOMA). A. TOURAINE and PAUL RENAULT, Bull. Soc. franç. de dermat. et syph. **43**:687, 1936.

The authors believe that cheilitis glandularis is of sufficient frequency to be called to the attention of physicians. One of the authors reported eleven cases of the disease in three years; of these five were instances of simple cheilitis (Puente's disease) and six were cases of suppurative cheilitis. In eight cases there was malignant degeneration.

Suppurative forms should be divided into two different clinical types. The first is the most frequent; it is characterized by chronic suppuration of the surface. The middle region of the lower lip is covered by dark, soft, adherent crusts which persist indefinitely. This suppuration, however, is exclusively on the surface and does not extend deeply into the glands. This type is known in Germany, where it is called Baelz' disease.

The second type of suppurating cheilitis, which is much more rare, was first described by Volkmann in 1870. In this type the mucous glands of the lip are swollen and emit a mucopurulent discharge. A deep furunculous inflammation is produced, which has a tendency to become fistulous and to discharge pus only occasionally. The term cheilitis apostematosa was proposed by Volkmann for this condition, although as a rule it is applied indifferently to the two types of suppurative cheilitis.

To distinguish these two distinct types the authors propose the name *chéilite glandulaire suppurée superficielle* or Baelz' disease for the superficial type. for the deep type they prefer the term *chéilite glandulaire suppurée profonde, chéilite glandulaire abcédée* or Volkmann's disease.

The authors report a case of the deep type occurring in an 84 year old man. The condition was complicated by squamous cell carcinoma.

MULTIPLE GLOMUS TUMORS OF THE TRUNK AND EXTREMITIES. A. TOURAINE, SOLENTE and PAUL RENAULT, Bull. Soc. franç. de dermat. et syph. **43**:736 (April) 1936.

The authors state that glomus tumors are not rare; Mason collected personally twenty-seven cases. In the case which the authors report the patient had multiple glomus tumors of an angiomatous form which developed at the age of 50 years. They appeared on the trunk and extremities, but the hands and especially the inguinal regions were spared. It was especially interesting that the patient's daughter had identical tumors. There were in all twenty-four tumors, varying in size from that of a hemp seed to from 12 to 15 mm. in diameter. The histologic picture was consistent with the diagnosis of the angiomatous form of glomus tumors described by Masson, the lesions being rich in blood vessels but poor in epithelioid and nerve tissue. The lack of nerve tissue explained the absence of spontaneous pain and the slight tenderness on palpation. Although the usual location of glomus tumor is subungual, Masson found a different distribution in thirteen of twenty-seven cases: in five the lesions occurred on the forearm, in three on the arm, in four on the thigh and in one on the leg. The fact that the patient's daughter had tumors suggested a hereditary factor in this condition.

CONJUNCTIVITIS WITH ADENOPATHY DUE TO THE VIRUS OF NICOLAS AND FAVRE'S DISEASE. C. LEVADITI, J. BOLLACK, G. BASCH and P. DESVIGNES, Bull. Soc. franç. de dermat. et syph. **43**:1238 (June) 1936.

The authors state that a patient aged 37 had a follicular conjunctivitis of the left eye of six months' duration accompanied with adenitis in the submaxillary region. The conjunctiva was infiltrated and had lost its suppleness. Both the bulbar and the palpebral portion were affected. There was no ulceration. The nodes were large, fluctuant and covered with reddened skin.

The Frei test was strongly positive, and an emulsion of the affected nodes injected intracerebrally into a monkey provoked lesions characteristic of lymphogranuloma venereum. The observation emphasizes the diversity of the manifestations of the disease.

INOCULATION INTO THE RABBIT OF THE CONTENTS OF BLISTERS OF PEMPHIGUS AND DERMATITIS HERPETIFORMIS. H. GOUGEROT and G. BROUET, Bull. Soc. franç. de dermat. et syph. **43**:1294 (June) 1936.

The authors cite the work of Urbach, Reiss and Wolfram concerning experimentation with animals in study of the bullous diseases.

In a case of dermatitis herpetiformis the first inoculation of the blister fluid into a rabbit's cornea resulted in rapid development of a paralytic syndrome, in twenty-seven days. The second inoculation caused keratitis in five days; this regressed completely in a month. Intravenous injection caused no symptoms.

In five other cases (two of dermatitis herpetiformis and three of pemphigus) the results were completely negative.

NODULAR ADENOMA OF THE TONGUE. H. GOUGEROT and OLGA ELIASCHEFF, Bull. Soc. franç. de dermat. et syph. **43**:1585 (Nov.) 1936.

The authors describe the clinical and histologic observations on a rare lesion of the tongue which it was impossible to diagnose clinically. The nodule was 15 mm. in diameter, indolent and without inflammation. It did not involve the mucosa and was situated near the tip of the tongue.

Histologically the mass was composed of hypertrophied mucous glands and showed no signs of malignant degeneration. LAYMON, Minneapolis.

VASOMOTOR UPSETS OF THE EXTREMITIES, CERTAIN ALLERGIC STATES OF MICROBIC ORIGIN IN INFANTS, AND FALSE ECZEMA. S. NOGUER-MORE, Paidoterapia **14**:615 (Nov.) 1935.

Noguer-More studied false eczema, so-called because it resembles eczema as far as the lesions of the skin appear but does not follow the course of eczema. He thinks a streptococcus produces dermatitis, starting on the cheeks, and that this serves as a substratum for the development of the vasomotor troubles. That this lesion is due to a local infection seems to be true, since it starts unilaterally. Later it spreads bilaterally, owing to sensitization to the streptococcus. To a certain point the vasomotor trouble may be considered specific. It generally becomes more specific when the local infection has persisted for some time; therefore it is conditioned, exaggerated and maintained through the infection itself. Vasomotor troubles of this type are different from regular eczema because they can be corrected without radical modification of the diet. Local treatment clears up the infection—application of iodine in alcohol and of a cream in a water base for cooling. Internally epinephrine or ephedrine is used.

SOME INFANTILE DERMATOSES IN RELATION TO CONGENITAL SYPHILIS. G. RAMÍREZ VALDES, Rev. mex. de puericultura **5**:904 (Nov.) 1934.

For purposes of study Ramirez Valdes divided syphilis into three phases: (1) from birth to between 3 and 4 months, (2) from 4 months to 3 years and (3) from 3 years to puberty. Each phase has its certain and its probable signs for the diagnosis of syphilis. The certain signs of the first period include: pemphigus, characterized by bullae localized preferably on palmar surfaces; seropurulent coryza; splenomegaly; syphilitic cutaneous manifestations; pseudoparalysis of Parrot; enlargement and swelling of the testicles, and a sign that is rare but characteristic of the disease, namely, a gummy or viscous ulcer of the umbilicus. The certain signs of the second period include craniotabes, protuberance of the frontal bone and pseudoleukemic anemia. The certain signs of the third period are the numerous dystrophies, such as malformation of the teeth (Hutchinson teeth) and of the nose (saddle nose), interstitial keratitis, bony lesions and deformities of the ear, such as perforation of the arch. The differential diagnosis takes account of alopecia, vitiligo, Hebra's prurigo and ichthyosis. Of five cases of alopecia studied, syphilis was shown in none; of ten cases of vitiligo, a family history of syphilis was recorded in three and positive Wassermann reactions in two; of twelve cases of Hebra's prurigo, a family history of syphilis was noted in three and Hutchinson teeth in three, and, of four cases of ichthyosis, probable syphilis in the mother was recorded in one. The author believes that syphilitic infection is capable of influencing with noticeable frequency some of the infantile dermatoses, but it is not easy in many cases to determine this relation clearly; sometimes it is proved only after treatment for syphilis has been carried out and has resulted in clearing up the dermatosis. Therefore, he believes that antisyphilitic therapy is indicated for patients with vitiligo, alopecia or prurigo after a careful study has been made in each case.

HERRON, Spokane, Wash. [AM. J. DIS. CHILD.]

PRIMARY DIPHTHERIA OF THE EXTERNAL GENITALIA OF YOUNG GIRLS. A. D. JAWOROWSKAJA, Dermat. Wchnschr. **102**:312 (March 14) 1936.

The literature in regard to primary diphtheria of the genitalia is briefly discussed, and four cases observed by the author are described. He points out that local therapy is required as well as general treatment.

A METHOD OF TRANSPORTING CULTURES OF FUNGI. H. HRUSZEK, Dermat. Wchnschr. **102**:317 (March 14) 1936.

Hruszek starts the culture in small tubes with a minimum of culture medium. The tubes are sealed in the Bunsen burner, and they can then be sent through the mail.

CANCER OF THE PENIS IN A SYPHILITIC PATIENT. A. D. JAWOROWSKAJA and J. G. LEWIT, Dermat. Wchnschr. **102**:353 (March 21) 1936.

A 58 year old man had a squamous cell epithelioma of the glans penis. He had had syphilis twenty years previously and had received insufficient therapy. Nevertheless, the Wassermann reaction of the blood was negative.

ETIOLOGY OF PITYRIASIS ROSEA. K. LUJZA HASPEL, Dermat. Wchnschr. **102**:357 (March 21) 1936.

The author observed six patients with pityriasis rosea in whom foci of infection (infected tonsils) were found. After the foci were removed the eruption cleared in from one to four days in each instance. Haspel concludes that pityriasis rosea is probably due to a focus of pyogenic infection. TAUSSIG, San Francisco.

MEANING OF PARALLERGY. G. BESSAU and H. FERNBACH, Jahrb. f. Kinderh. **145**: 61 (Aug.) 1935.

Bessau and Fernbach take issue with those who consider parallergy anything other than a specific reaction of the organism induced by excitants different from the primary allergen. The sensitivity against the bouillon of tuberculin rather than against the specific substance of the tubercle bacillus, in their opinion, may be taken as an example of parallergy. They feel that the claims of Moro and Keller that it is on the basis of a true allergic reaction against the tubercle bacillus are unproved.

IMMEDIATE AND DELAYED CUTANEOUS REACTIONS. O. TEZNER, Jahrb. f. Kinderh. **145**:86 (Aug.) 1935.

Tezner feels that the results of his experiments, which are reported, correspond with the results of Burchard's experiments with egg white. They both came to the conclusion that the delayed papular reaction is found only in parenterally sensitized children while the immediate cutaneous reaction is found only in children with a true idiosyncrasy.

LANDAU, Hannibal, Mo. [AM. J. DIS. CHILD.]

THE TIME OF APPEARANCE OF THE SPIROCHETES OF SYPHILIS IN REGIONAL LYMPH NODES. T. TANI, K. OGIUTI, H. HUTAKI and I. OYA, Zentralbl. f. Bakt. (Abt. 1) **134**:54, 1935.

Emulsions of spirochetes of syphilis were rubbed into scarified areas in the scrotal sacs of albino rabbits. The organisms were demonstrated in regional lymph nodes as early as five minutes later and in the blood within one hour. The spleen was spirochete-free for at least five days.

Local treatment of the infected scarified area was useless when washing with soap solution was tried, whereas a salve (presumably mercurial) protected two of four rabbits when applied immediately but was without effect when used fifteen minutes after infection.

CANNON, Chicago. [ARCH. PATH.]

LOCAL IMMUNIZATION AGAINST INFECTIONS OF THE SKIN WITH STAPHYLOCOCCI. F. KLOPSTOCK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **86**:213, 1935.

Cutaneous inunctions of staphylococcus vaccines into rabbits were followed after proper intervals by intracutaneous injections of the bacteria, with only slight and irregular evidence of protection. Application of the bacterial suspension in the form of an ointment immediately after the injection of the bacteria into the skin failed to have any influence on the course of the infection.

DAVIDSOHN, New York. [ARCH. PATH.]

KAPOSI'S DISEASE AS A SYSTEMIC ANGIOMATOSIS. F. J. LANG and L. HASLHOFER, Ztschr. f. Krebsforsch. **42**:68, 1935.

Probably few apparently neoplastic diseases have been more variously interpreted than the entity commonly known as Kaposi's disease. It has been regarded as sarcoma of connective tissue origin, as a malignant endothelial growth, as a malignant vascular growth, etc. There are described here the progressive lesions in two cases, and from them the writers conclude that the disease is primarily a vascular alteration, which takes the form of new capillary formation along with overgrowth of the endothelium of the capillaries and smaller vessels. Apparent internal metastases are regarded by them as the results of similar changes in those sites. In their opinion Kaposi's disease is a systemic hemangiomatosis, with the possibility, in the later stages, of perivascular connective tissue overgrowth and secondary vascular degeneration which may lead to eventual healing.

EGGERS, Omaha. [ARCH. PATH.]

INFLUENCE OF ECZEMATOUS CHANGE IN THE SKIN ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT AND ON THE RESORPTION ABILITY OF THE INTESTINES. K. KITAMURA, K. NARAHARA, N. TANAE and T. HONDA, Jap. J. Dermat. & Urol. **40**:103 (Sept.) 1936.

Roentgenologic examination of the gastro-intestinal tract of the rabbit before and after production of dermatitis by croton oil revealed reduction in motility during the acute stage and gradual increase in the subacute stage, reaching frequently a greater degree than under normal circumstances. Experiments with trypan blue showed an increase in resorption by the intestinal wall during the dermatitis and a return to normal in the stage of healing. There was also diminished excretion of phenolsulfonphthalein in the urine, indicating a diminished passage from the gastro-intestinal tract into the circulation.

INFLUENCE OF ECZEMATOUS PROCESSES ON THE LIVER (CONTENTS OF GLYCOGEN AND FAT IN THE LIVER IN EXPERIMENTAL DERMATITIS). N. TANAE, Jap. J. Dermat. & Urol. **40**:105 (Sept.) 1936.

After having produced dermatitis in rabbits by means of croton oil Tanae examined microscopically the changes in the liver of the killed animals. He observed complete disappearance of the glycogen and a peculiar deposit of fat in the parenchymatous cells during the first and second weeks of the dermatitis. After the dermatitis had healed he found that the glycogen content was normal and that the deposit of fat had disappeared.

CONTRIBUTION TO THE PATHOGENESIS OF ANGIOMA. S. YAMADA, Jap. J. Dermat. & Urol. **40**:109 (Sept.) 1936.

After the introduction of a solution of histamine into the skin of persons with numerous dermatoses there was no difference in the time of appearance of the wheals in the affected and in the normal surrounding skin. However, in cases of cavernous hemangioma no typical wheal could be produced in the affected area. In cases of simple hemangioma the wheal in the affected area was smaller or appeared later than the wheal in the surrounding healthy skin. Yamada believes that this finding corroborates the opinion expressed by Buschke that angioma is due to congenital aplasia or hypoplasia of the vasoconstrictor nerves, which produces an increased blood supply and leads to dilatation and new formation of vessels.

A CASE OF AXILLARY ADENITIS DUE TO EXTRAGENITAL INFECTION WITH LYMPHOGRANULOMA VENEREUM ASSOCIATED WITH FREQUENCY OF URINATION. S. TANAHASI, Jap. J. Dermat. & Urol. **40**:113 (Sept.) 1936.

Tanahasi reports a case of lymphogranuloma venereum affecting the axillary glands in a 45 year old man. As an assistant to a venereologist, he contracted this infection through handling patients with inguinal buboes. The place of entrance of the virus was probably an opening in the skin of the tip of the right index finger, as the tissue at this point was tender for some time before the axillary adenitis developed. The tumor was as large as a fist and unevenly nodular, consisting of matted glands. The pain and tenderness were moderate. The skin over the tumor was livid, and there were a few small abscesses and a large confluent abscess. The patient had remittent fever, general malaise, anorexia and loss of weight. An intradermal test with the Frei antigen was positive, and the pus from the tumor yielded an effective Frei antigen. Five intravenous injections of an antimony preparation and daily exposures to infra-red rays produced an almost complete cure in two and one-half months.

The patient complained also of frequency of urination, although the urine was perfectly normal. This symptom was observed by the author in the majority of cases of lymphogranuloma venereum involving the inguinal region. It started, as a rule, in the beginning of the illness and improved gradually without any treatment.

A CASE OF VERRUCOUS NEVI ASSOCIATED WITH BASAL CELL EPITHELIOMAS, BOWEN'S DISEASE AND SQUAMOUS CELL EPITHELIOMA. I. TÔYAMA and R. KOJIMA, Jap. J. Dermat. & Urol. **40**:116 (Sept.) 1936.

Tôyama and Kojima report the case of a 47 year old woman with a generalized eruption, which started at the age of 10 years and gradually extended all over the body. The eruption consisted of pale brown, flat, slightly elevated papules, which were particularly numerous on the upper and lower extremities and looked like epidermodysplasia verruciformis of Lewandowsky or verrucosis generalisata of Hoffman. On the back of the trunk there were pigmented macules. Histologically, papillomatosis, acanthosis and hyperkeratosis were observed. On the abdomen there were violaceous-black bean-sized oval papules, the microscopic examination of which revealed basal cell epithelioma of Krompecher. The crusted papular, almost annular lesions on the face and sternum revealed under the microscope the picture of Bowen's disease. The walnut-sized tumor near the inner canthus of the left eye presented the pathologic picture of typical squamous cell epithelioma. The authors believe that the malignant lesions developed from the generalized verrucous papules, which seemed to be nevi.

BLOOM, New York.

# Society Transactions

## MANHATTAN DERMATOLOGIC SOCIETY

ISADORE ROSEN, M.D., *Chairman*

*Jan. 12, 1937*

MIHRAN B. PAROUNAGIAN, M.D., *Secretary*

**Eczema.** Presented by DR. FRED WISE.

S. W., a Jewish dentist aged 41, born in Russia, was seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Sept. 4, 1936. He had a generalized eruption which began in January 1936 as a pea-sized area of involvement on the abdomen and inguinal region and which gradually spread to the rest of the body. In 1926 he had generalized dermatitis, which cleared up completely when treated with juniper tar. The family history is irrelevant.

In September 1936 there was an erythematous scaling vesicular dermatitis occurring in patches and plaques on the face, chest, back, abdomen and extremities; the patches varied in size from that of a pea to that of a silver dollar, and almost the entire back was covered. The rectal temperature was 100 F., and the temperature remained elevated for two weeks, the highest reading being 104 F. A general physical examination failed to disclose either an accompanying disease or the cause of the increase in temperature.

The treatment consisted of doses of ¼ skin unit (75 roentgens) of roentgen radiation to the involved areas and of topical applications of a variety of soothing wet dressings, lotions and ointments. Potassium permanganate baths, arsenic-poor, egg-free and elimination diets and administration of oral sedatives were also employed. There was little response to treatment.

The results of a blood count, a culture of blood obtained during the febrile period, a determination of the basal metabolic rate, an analysis of the content of the stomach, cultures of the bile, roentgen examination of the chest and estimation of the arsenic content of the urine were noninformative.

Since the patient was discharged from the hospital on Oct. 31, 1936, fresh papular scaly infiltrated lesions have appeared on the limbs and face, and early in January 1937 the whole body was covered. Further topical and roentgen therapy was unavailing.

### DISCUSSION

DR. MIHRAN B. PAROUNAGIAN: I suggest the diagnosis of lichen planus on account of the color, generalized distribution, absence of exudation and extreme itching.

DR. GEORGE C. ANDREWS: This patient's condition reminds me of that of a Greek man whose case was reported in the ARCHIVES (**32**:963 [Dec.] 1935; **33**:774 [April] 1936). I presented that man at a meeting of the Section of Dermatology and Syphilis of the New York Academy of Medicine. He had been treated at various clinics for eight years, and he is still being treated. My co-workers and I have not been able to make a differential diagnosis between mycosis fungoides and eczema.

DR. PAUL E. BECHET: For reasons too numerous to mention mycosis fungoides does not seem to me to be a plausible diagnosis. At present, one must remain content with the diagnosis of eczema, but in my opinion the eruption may eventually be found to be associated with a leukemic or an aleukemic state.

**Dermatitis Lichenoides Chronica Atrophicans (Czillag).** Presented by Dr. David L. Satenstein.

M. W., a girl aged 17, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, has had a lesion on the left upper eyelid for one year. It started as a small white area and has slowly increased in size. At no time has there been any redness in the lesion. At times there is moderate itching. The urinalysis, the Wassermann and the Kahn test and tuberculin tests gave negative results. Roentgenograms of the chest showed no abnormalities. At present there is a dime-sized white atrophic lesion at the inner canthus of the left eye. It is well defined and somewhat round. The area is wrinkled, and there are several pinpoint spots in the interior of the plaque.

DISCUSSION

Dr. Isadore Rosen: I hesitate to make a diagnosis of dermatitis lichenoides chronica atrophicans. I fail to find any clinical evidence of that disease. The patient presents an isolated patch which may or may not be atrophic. It may fit in with a localized scleroderma.

**Rosacea-Like Tuberculid of Lewandowsky.** Presented by Dr. J. Frank Fraser.

J. G., a woman aged 27, was presented at the meeting of the New York Dermatological Society on Dec. 15, 1936 (Arch. Dermat. & Syph. **36**:392 (Aug.) 1937).

DISCUSSION

Dr. Paul Gross (by invitation): Of the two patients presented tonight with the diagnosis of rosacea-like tuberculid of Lewandowsky, this one showed a strongly positive reaction to tuberculin while the other had a negative reaction. This and some clinical and histologic factors seem to point to the fact that both papulonecrotic tuberculid associated with hypersensitivity to tuberculin and miliary lupus of the face (usually associated with hyposensitivity) may assume the rosacea-like picture.

Dr. Paul E. Bechet: I wish to discuss this case from a clinical standpoint. The girl does not show rosacea. She has copper-red scattered lesions over the face, with here and there some follicular atrophy. Before the publication of Lewandowsky's report, in 1917, this condition was generally classified either as lupus vulgaris or as tuberculid. In my opinion, the frequency with which Lewandowsky's disease has been reported recently will diminish greatly in years to come, and many of the conditions that are reported as that disease today will eventually again be classed with the tuberculids or with miliary lupus. Lewandowsky's tuberculid may or may not prove to be a clinical entity. It is therefore important to present as many examples of this eruption as possible in the hope that the observation of many cases will eventually bring out clinical data as to visual characteristics typical of the disease, corroborating the microscopic diagnosis.

**A Case for Diagnosis (Erythroplasia?).** Presented by Dr. David L. Satenstein.

A. S., a man aged 48, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, has been troubled for the past nine months with lesions on the penis. There are considerable burning and itching. He states that a few lesions on the shaft of the penis healed spontaneously but that new ones developed. Within the last two months lesions appeared on the scrotum. The Wassermann and the Kahn test and urinalysis gave negative results. On the glans penis is a well defined round lesion about 2 cm. in diameter. The entire surface is eroded, and there is a clear red granulating base. On the posterior surface of the glans are several small similar lesions, but these are covered by a thin crust. On the shaft of the penis are three lesions 1 cm. in diameter, which

are slightly raised, partly scaly and partly covered by a crust. Also, there are two lesions of the same type on the scrotum. All the lesions ooze. The inguinal lymph nodes are not palpable.

DISCUSSION

DR. FRED WISE: I examined the lesions of this patient in 1932. At that time he had an erythematous dermatitis of the penis, possibly a ringworm infection. The lesions which he now presents impress me as being eczema which has been either irritated or inadequately treated by the patient. I should not venture the clinical diagnosis of erythroplasia with reference to the lesion on the glans penis. A histologic examination will be necessary.

DR. ISADORE ROSEN: The clinical features present tonight suggest that the primary lesion was bullous, and I should be inclined to consider the possibility of pemphigus vulgaris.

**Tuberculosis Verrucosa Cutis.** Presented by DR. FRED WISE.

A. C., a schoolboy aged 12 years, born in the United States, was seen on Dec. 1, 1936, at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, exhibiting an eruption in the region of the right ankle which appeared when he was 2 years old. When the patient was 3 months old there developed in the right axilla a hard red lesion, which soon softened and was opened; thereafter, it drained for four months before healing. From the age of 9 months to about 3½ years the child had similar lesions which developed on different areas of the skin. Each was opened, and some remained open for periods as long as three years. Since he was 2 years old the first phalanx of the left middle finger has been swollen. The fungating lesion which is now present also appeared on the external surface of the right ankle when he was 2 years old. It increased rapidly in size and now measures approximately 4 cm. in diameter. For the past nine or ten years it has remained stationary. There are slightly depigmented scars in the right axilla, on the dorsum of each hand, on the external surface of the right forearm and on the right shin. The family history is not suggestive of syphilis or of tuberculosis. Tuberculin tests were strongly positive, and the Wassermann and the Kahn test were negative. A roentgen examination of the left middle finger showed osteochondritis and periostitis of a low grade.

DISCUSSION

DR. MIHRAN B. PAROUNAGIAN: My impression is that the lesion on the lower portion of the leg is tuberculous, but the patient may have congenital syphilis, as he has certain stigmas suggestive of that condition.

DR. LUDWIG B. OULMANN: Manifestations such as those present in this case are observed when a tuberculous condition is associated with congenital syphilis. However, a negative Wassermann reaction in a case in which active lesions have been present for years excludes syphilis. The lesion on the ankle is, in my opinion, not tuberculosis verrucosa but scrofuloderma.

**Xeroderma Pigmentosum in Two Brothers.** Presented by DR. PAUL E. BECHET.

A. B., aged 10 years, and G. B., aged 12 years, two brothers, were presented before this society by Dr. Oulmann on March 10, 1931, with this diagnosis, and the cases were reported in the ARCHIVES (**24**:683 [Oct.] 1931). At that time the diagnosis was unanimously accepted, though all the members present agreed that the lesions were exceedingly mild. The children are again presented because of the marked aggravation of the disease since the first presentation. Both were born in the United States. At the time they were presented by Dr. Oulmann the patients were only freckled and had a few scaly spots here and there. Both boys now have on the face, on the upper portion of the chest and on the hands innumerable dark brown spots with inflammatory scaly areas. Throughout these

areas atrophic and even scarred and telangiectatic patches occur. There are many lesions with pearly borders on the nose, and a few are already undergoing central ulceration. The younger brother, who was the least affected six years ago, shows more serious epitheliomatous changes than the elder. Microscopic examination showed the epidermis to be markedly acanthotic and irregular. Its surface was covered by a moderate, closely laminated horny layer, which in part was parakeratotic. The vessels of the upper portion of the cutis were moderately dilated, and there was a diffuse cellular infiltrate composed of small round cells, wandering connective tissue and polymorphonuclear leukocytes. Sections of the lesions showing clinical epitheliomatous changes exhibited a typical microscopic picture of epithelioma of the basal cell type.

DISCUSSION

DR. LUDWIG B. OULMANN: These two boys were presented by me in 1931, and I saw them from time to time until last year. At the time of the first presentation the condition was regarded as extremely mild, especially in the younger one, who today shows cancerous changes. This proves how difficult it is to make a prognosis in cases of apparently mild xeroderma.

DR. PAUL E. BECHET: These patients are again presented because of the marked aggravation of the disease since their last presentation, six years ago. It is also interesting to note the lack of familial history, the mother being certain that no other member of the family was ever affected.

**Rosacea-Like Tuberculid of Lewandowsky.** Presented by DR. J. FRANK FRASER.

C. L., a man aged 26, was seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with an eruption of seven years' duration. There were many fine papules scattered over his face and forehead and a few lesions on his knees. At present the patient has many slightly indurated small brownish red papules on the forehead, cheeks, nose and chin which are in general confined to the middle two thirds of the face, erythema being present throughout the involved area. There are no scars or areas of necrosis. There are follicular papules on the knees. He has itching most of the time. The lesions appear and disappear, clearing almost entirely in the summer. The patient has always done manual labor outdoors. He has lost no weight and has had an average number of colds. There is no history of tuberculosis in the family.

The histologic examination showed rosacea-like tuberculid of Lewandowsky. The tuberculin tests, urinalysis and Wassermann test gave negative results. Roentgen examination of the chest showed a relatively small heart and old thickening of the hilus and root of one lung with slight interlobar thickening of the pleura.

**Kaposi's Sarcoma.** Presented by DR. ISADORE ROSEN.

J. C., a man aged 49, a Puerto Rican, a dishwasher, has been complaining for the past nine and one-half years of intermittent attacks of pain and redness of both lower extremities. The eruption first began on the legs and was purpuric. The eruption on the trunk is said to have appeared seven years ago. The patient was treated at the New York Skin and Cancer Hospital in 1928, where several microscopic examinations of material from lesions on the lower extremities showed idiopathic hemorrhagic sarcoma of Kaposi. He returned to Puerto Rico, and in 1931 he was said to have filariasis and was hospitalized for three months. The patient presented himself at the Mount Sinai Hospital in the early part of 1936 with lesions of Kaposi's sarcoma on both lower extremities, especially on the posterior aspects of the legs and ankles and on the dorsa of the feet. There were numerous pea-sized and bean-sized lesions scattered over the trunk anteriorly

and posteriorly, most of which showed little variation in color from the normal skin. Here and there a lesion with slight hemorrhage or pigmentation could be detected. The blood count showed 80 per cent hemoglobin, 5,100,000 red cells and 9,000 white cells. There were 230,000 platelets. The differential cell count showed 46 per cent nonsegmented forms, 3 per cent segmented forms, 36 per cent lymphocytes; 8 per cent monocytes and 7 per cent eosinophils. The Wassermann and the Kahn test were negative. A histologic examination made on Dec. 18, 1936, showed marked hyperkeratosis and flattened papillary bodies. Throughout the middle portion of the cutis there were many thin-walled blood vessels like angiomas. There was little proliferation of the adventitial cells but together with the hemorrhage there was enough to justify a diagnosis of early stage of Kaposi's sarcoma.

DISCUSSION

DR. FRED WISE: The eruption is especially interesting on account of the nonpigmented elevated lesions which do not resemble the clinical features of Kaposi's sarcoma. It would seem almost impossible to make a clinical diagnosis on inspection of these lesions alone. A patient at the clinic presented generalized lesions of this disease, but the clinical diagnosis could readily be made on inspection of any of the individual lesions.

DR. PAUL GROSS (by invitation): There is a fundamental question involved in this case. The lesions on the trunk, in appearance and distribution, suggest true metastatic tumors of the skin. The disseminated lesions in Kaposi's sarcoma have been regarded as multiple, that is coordinated, lesions, even if they involve the intestines. This case certainly creates a different impression.

DR. J. FRANK FRASER: The histologic changes in the metastatic lesions reported by Kaposi were characteristic of round cell sarcoma.

DR. ISADORE ROSEN: I presented this case because of the unusual clinical features, which I have never seen associated with this disease. I agree with Dr. Wise that one could not base a diagnosis on the lesions of the trunk without seeing those on the lower extremities.

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ISADORE ROSEN, M.D., *Chairman*

*Feb. 9, 1937*

MIHRAN B. PAROUNAGIAN, M.D., *Secretary*

**Keloid Due to a Burn.** Presented by DR. J. FRANK FRASER.

M. C., a woman aged 60, has a keloidal scar on the dorsal aspects of the hand and wrist which resulted from an accidental contact with hot candy. The duration of her condition is five months. She is presented principally for suggestions as to therapy.

DISCUSSION

DR. LUDWIG B. OULMANN: In some cases I have seen good results from treatment with solid carbon dioxide followed by roentgen radiation.

DR. MIHRAN B. PAROUNAGIAN: I suggest ultraviolet irradiation and massage with cold cream or boric acid ointment.

DR. MAX SCHEER: I should use roentgen radiation. It is while the keloidal tissue is soft that good results from roentgen treatment are obtained. The longer one waits, the poorer the results will be. I should give ¾ skin unit (225 roentgens) of unfiltered radiation once every month until three or four treatments were given. I do not think that telangiectasia would result from that dose. I should protect the normal areas with paste containing bismuth and with lead.

DR. GEORGE C. ANDREWS: I think that a good result will follow if nothing is done except give nature some time. If the keloid does not decrease satisfactorily, a few doses of roentgen radiation will give a good result. Nowadays, most of the surgeons who excise keloids give treatment with roentgen radiation before as well as after the operation.

DR. ANTHONY C. CIPOLLARO: I wish to indorse the remarks made by Dr. Scheer regarding the treatment of this condition. If the lesion should fail to respond satisfactorily to that amount of radiation, treatment with galvanism might prove efficacious.

DR. PAUL E. BECHET: In my opinion, roentgen radiation gives excellent results in treatment of recent keloids caused by burns. Within the year I have treated a linear keloid about 25 mm. long by 3 mm. wide which developed immediately after a burn from contact with a hot radiator. The keloid was of an angry red color and greatly raised, and the pressure it produced on the nerve endings caused pain. The result of roentgen therapy has been excellent. At the time of the patient's last visit the keloid had been replaced by a perfectly flat white scar, and the pain had disappeared.

DR. J. FRANK FRASER: I disagree with the idea that roentgen radiation should be used immediately after surgical removal. Has it been shown that roentgen therapy prevents the development of keloids? If it does not, the treatment should be delayed until the appearance of the keloid.

**A Case for Diagnosis (Varix?).** Presented by DR. MIHRAN B. PAROUNAGIAN.

A. M., a girl aged 21, is presented because of a condition which began about six years ago. The lesions, which are limited to the right foot, consist of tumor-like masses distributed as follows: One lesion involves the dorsum of the third toe of the right foot and the plantar surface of the second and third toes, and one is on the outer aspect of the foot, below the malleolus. A number of dilated veins are present in this region. The lesion on the third toe is a mass resembling a supernumerary toe; it is firm and inconveniences the patient in wearing shoes. The other lesions are smaller but more numerous. Some of the lesions have a bluish tinge. The patient's mother states that at times they are painful. The family history is irrelevant. The patient's birth was abnormal, she is undernourished, and at the age of 2 years she could hardly sit up. Her mentality is retarded, and at present she is unable to speak, read or write. She looks about half her age. The roentgen examination showed phlebitis with calcium deposits. The Wassermann reaction was negative.

DISCUSSION

DR. GEORGE C. ANDREWS: There is a large varix on the right leg, which if cut into would cause a bad hemorrhage. I think that a solution of sodium morrhuate should be injected into this varix before any attempt to excise the papillomatous lesions on the toe is made. The girl is a deaf mute, and that condition may be linked up with the other congenital anomalies.

DR. MIHRAN B. PAROUNAGIAN: I consider the condition to be surgical and not dermatologic. I wanted the opinion of the members. I have never seen an abnormality like this, and I could not diagnose it.

**Steatocystoma Multiplex Congenitale.** Presented by DR. DAVID L. SATENSTEIN.

E. M., a woman aged 39, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, has numerous cutaneous tumors. According to the history, the following members of her family have the same condition: her father, her father's sister, one brother who has three children none of whom is affected, one brother who has one daughter not affected, one sister

whose children are not affected and one brother who has no children. The patient's son and one daughter are affected, but one daughter is not. There were thirteen children in the patient's family. Two brothers were killed while working on the railroad, and one of these had suffered from ichthyosis. Four children died when they were but a few days old. Two are living who are normal. The mother died of cancer of the stomach with metastasis.

In all the patient's relatives in whom the skin is involved the condition was present at birth. There have never been any subjective symptoms. The parts most affected are the face, the forehead, the scalp, the chest, the back and the extremities. The abdomen and the lower portion of the back are free from lesions in all the patients. One of the brothers has lesions on the legs, and the others have not; the lesions of the brother whose legs are involved are much larger than those of the other patients.

The cases of this patient, her son, aged 15, and her daughter, aged 19, have been studied more completely. The leesions vary in size from that of the head of a pin to that of a large pea; they are skin colored, yellow or brown, and some are almost black. Some of the lesions are soft; others are firm. From some a cheesy material can be expressed. Histologic examination showed atheroma.

DISCUSSION

DR. GEORGE C. ANDREWS: I have a patient with this condition whom I have been treating for some time, and the thing which impresses me is that the material which comes out of these cysts is not like that discharged by other cysts. It is more like butter.

**A Case for Diagnosis (Pemphigus?).** Presented by DR. J. FRANK FRASER.

V. B., a physician aged 37, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, has an eruption of four months' duration. Two years ago he had impetigo contagiosa (?) of the scalp, which lasted one month. This was treated with three subfractional doses of roentgen radiation (38 roentgens) at weekly intervals, and apparently cleared up. Four months ago the eruption on the scalp recurred and spread to the shoulders. About two months ago the patient had the grip, during which the lesions spread to the back and front of the chest and abdomen. The extremities were comparatively free. He had subjective symptoms consisting of burning and itching which disturbed his sleep. The lesions started as pea-sized denuded patches with no erythema. Later an erythematous base developed, and the lesions became vesicular. They consist of clear vesicles and small bullae. Histologic examination showed only a vesicular dermatitis. The patient took three or four doses of acetylsalicylic acid for his grip. He received five daily injections and pills of sodium thiosulfate with no relief. He also received three fractional doses of roentgen radiation (75 roentgens) at weekly intervals, concurrently with five daily injections of sodium arsenate and twenty pills of 6 grains (0.39 Gm.) of plasmochin, and some relief followed. There are no lesions on the mucous membranes.

DISCUSSION

DR. PAUL E. BECHET: I do not think that it is possible to make any definite diagnosis at present, but I feel sure that this eruption will eventually develop into a mild but typical pemphigus vulgaris.

DR. LUDWIG B. OULMANN: One should consider the possibility of seborrheic eczema accompanied by bullae.

DR. MIHRAN B. PAROUNAGIAN: I favor the diagnosis of seborrheic eczema. I exclude Duhring's disease because of the absence of lesions on typical locations, of grouping and of pruritus. As to the diagnosis of pemphigus, it should be borne in mind that there are no lesions on the mucous membranes and no bullae

or vesicles and that the patient states that no such lesions have ever been present. The location of the lesions on the sternum and intrascapular regions suggests seborrheic eczema.

DR. MAX SCHEER: I have never seen a bullous seborrheic eczema.

DR. ANTHONY C. CIPOLLARO: This case was presented because the clinical picture is not definite for any one dermatosis. All the various diseases that produce bullae have been mentioned. My clinical diagnosis, based on the distribution, history of the evolution and type of lesions, is pemphigus vulgaris.

DR. ISADORE ROSEN: I agree with those who believe that this patient has pemphigus. The eruption undoubtedly is bullous. Although bullae may not be evident clinically, they probably rupture rapidly after they appear. A persistent bullous eruption which does not respond to the ordinary methods of therapy should suggest pemphigus.

**Tertiary Syphilis (?).** Presented by DR. ANTHONY C. CIPOLLARO.

M. F. a woman aged 33, born in the United States was seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Oct. 27, 1936, with an eruption involving the posterior aspect of the right leg of five weeks' duration. The contour of the lesion is irregular and is made up of many small punched-out ulcers involving an area measuring approximately 4 by 3 inches (10 by 7.5 cm.). The condition has spread gradually. The patient is married and has two children, who are living and well. Her husband is living and well. She has never had any miscarriages. She has received three injections of a bismuth preparation and one injection of neoarsphenamine. Wassermann and Kahn tests made before and after she received one injection of neoarsphenamine were negative. The lesions have not responded to either local or systemic treatment. There is no history of ingestion of drugs.

DISCUSSION

DR. MAX SCHEER: I suggest the diagnosis of chronic ulcerated pyoderma resembling syphilis.

DR. PAUL E. BECHET: I wish to inquire of Dr. Cipollaro whether the woman shows any signs of hysteria, as the possibility of an artefact must be considered. An occlusive dressing, which could not be removed by the patient, might prove or disprove this suggestion. Syphilis is another possibility to bear in mind. She has not had sufficient treatment to rule out that diagnosis. The fact that the Wassermann reaction is negative proves nothing, as every one knows that that test is negative in approximately 25 per cent of cases of tertiary syphilis. This is an interesting case, and the diagnosis is doubtful.

DR. MIHRAN B. PAROUNAGIAN: I hardly agree with the diagnosis of tertiary syphilis. The location is not typical, the clinical picture is not that of tertiary syphilis and the serologic reaction is negative. One of the following two diagnoses is suggested: tuberculosis or blastomycosis. I do not think that the condition is an artefact or a drug eruption.

DR. GEORGE C. ANDREWS: No one is satisfied with the diagnosis of syphilis in this case. The duration of only six months is short for an ulcerative type of tuberculosis to cause a lesion of such size. It seems to me that the diagnosis lies between some fungous infection like blastomycosis or actinomycosis or chronic serpiginous pyoderma. In the middle of the lesion there is a verrucous appearance that is seen in blastomycosis.

**A Case for Diagnosis (Purpura Annularis Telangiectodes?).** Presented by DR. MAX SCHEER.

## CHICAGO DERMATOLOGICAL SOCIETY

MAX S. WIEN, M.D., *President*

*Jan. 20, 1937*

RUBEN NOMLAND, M.D., *Secretary*

**Sarcoid (Schaumann's Syndrome).** Presented by DR. OLIVER S. ORMSBY.

F. M., a woman aged 29, presents a cutaneous disease of five years' duration. When first seen she had brown plaques on the face, the upper part of the left arm and the left ring finger. The first spot appeared on the forehead five years ago, and new ones have gradually developed.

Examination shows brownish maculopapular and superficial nodular lesions on the forehead and cheeks. These vary in size from that of a match head to that of a pea and larger. A number of the lesions are violaceous. They are moderately elevated and under presure with the diascope present numerous pinhead-sized brown discolorations. In addition, the distal interphalangeal joint of the left ring finger shows some enlargement and a bluish discoloration. Lymphadenitis is indicated by a walnut-sized gland in the axilla and a smaller gland in the postauricular region. No clinical changes are noted in the tonsils. The circulation in both the upper and the lower extremities resembles that associated with chilblains.

A differential leukocyte count showed that the monocytes were within normal limits (4 per cent).

Treatment for two and a half months with gold sodium thiosulfate has reduced the infiltration and made the lesions inactive, but none have disappeared.

**Tuberculosis Cutis (Type ?); Annular Sarcoid (?).** Presented by DR. CLARK W. FINNERUD.

E. B. F., a physician aged 50, has an eruption on the back of the neck of about ten months' duration, which was first noticed by his wife. There are no subjective symptoms. About a year before the appearance of this eruption the patient first noticed a patchy redness of the back of the left hand, which was followed in the course of six weeks or so by a similar eruption on the back of the right hand. The eruption disappeared from the left hand about three months ago, but traces of it persist on the right. The patient gave a history of a slight bronchial disturbance of several years' duration, but no definite evidence of tuberculosis has ever been elicited. It has occurred to him that possibly the eruption on the hands has been precipitated by the rubbing of the cuffs of the sleeves of his coat on these areas, and that on the neck by the rubbing of his collar. He has also considered the possibility that light was an etiologic factor.

When I first examined the eruption on the neck, about six months ago, its clinical appearance was much like that of pseudoxanthoma elasticum. An examination of the eyegrounds for angioid streaks gave negative results.

When the patient was seen about a month ago the eruption on the neck showed not only reticulation and a slight papular element similar to pseudoxanthoma elasticum, but also some marginate superficial coin-sized and smaller smooth and rather firm nodular lesions of a little lighter color than the surrounding normal skin. The lesions of the backs of the hands were scarcely discernible and practically devoid of infiltration.

A section removed from one of the lesions on the neck, of somewhat scalloped margination, showed nests of epithelioid cells throughout the upper half of the corium; in the center of some of the nests were giant cells, both of the Langhans and of the foreign body type. About some of the nests was a scattering of plasma cells and lymphocytes. No inoculation of animals or tuberculin tests have yet been performed.

**Sarcoid.** Presented by Dr. T. K. Lawless.

H. M., aged 37, whose previous history shows nothing remarkable, presents an eruption which began seven years ago as a small papule on the nose. This was followed by nodules on the right arm. The extension of the process has been continuous so far as size of lesions and areas involved is concerned. The lesions vary in form from papules to plaques 9 by 11 cm. They are dull reddish brown, infiltrated, painless except on pressure and bilateral, with special involvement of the nose and the arms.

The Wassermann and Kahn tests, the tuberculin test and urinalysis gave negative results. Inoculation of animals showed negative results. The blood count was within normal range.

Roentgenograms of the chest showed considerable peribronchial thickening, with calcified glands in the hilus. Scattered throughout the pulmonary tissue were many miliary areas of markedly increased density. These findings are consistent with those seen in sarcoid. The microscopic slides shown are characteristic.

Four years ago an associated spasmodic hoarseness was noted. This is still present.

**Tuberculosis Cutis (Type ?); Lupus Vulgaris (?).** Presented by Dr. Clark W. Finnerud.

M. V., a Filipino aged 40, attendant in a Pullman car, presents a soft nodule the size of a finger-nail on the posterior wall of the right nostril, immediately within the vestibule, of two months' duration and devoid of subjective symptoms. The lesion was noticed by a rhinologist whom the patient consulted because of recurrent colds. The patient lived in the Philippine Islands from birth until 1919.

Examination reveals in the nostril a rather soft cribriform nodule the size of a large pea. Two pinhead-sized or smaller pustules are seen on its posterior border. Cultures and examination with potassium hydroxide of pus from these lesions revealed no blastomycetes or other yeasts.

Smears of material obtained by puncture of the lesion and of material from the interior of the nose elsewhere revealed no lepra or other acid-fast bacilli. The Wassermann and Kahn tests gave negative results.

Examination of histologic sections showed a granulomatous infiltrate throughout the corium, consisting of nests of plasma cells, epithelioid cells, giant cells and lymphocytes. There were no foam cells suggestive of lepra, and Ziehl-Neelsen stains of the tissue revealed no acid-fast bacilli.

**Sarcoid.** Presented by Dr. Clark W. Finnerud and Dr. Ralph H. Scull (by invitation).

C. M., a Negress aged 23, when first seen on April 23, 1935, presented nodular lesions ranging in size from that of a pinhead to that of a pea and of lighter color than the normal skin. These appeared around the mouth, the nose and the eyes. Annular lesions, ranging in size from that of a dime to that of a quarter, were present in the scalp.

Histologic examination of the lesions on the face and the scalp at that time showed tubercles composed of round and epithelioid cells.

Treatment with old tuberculin had cleared up all the lesions except a few around the alae of the nose, when the patient stopped treatment.

She returned in December 1936, with a recurrence in the same areas. The lesions were the same except those around the alae of the nose, which were larger and more erythematous, and showed a tendency to coalescence.

Serologic tests gave negative results.

Microscopic sections of material taken from the face when the patient was first seen are presented.

Discussion

Dr. H. E. Michelson, Minneapolis: This condition presents such a gigantic problem that it is impossible to discuss it adequately without taking too much

time. Gradually more and better observations on tuberculosis of the skin are being amassed, but it seems impossible to come to a perfect agreement because the subject is too large for seeing eye to eye. It seems impossible to make a classification that is acceptable to all. In some of the cases observed this afternoon one must review the serologic, pathologic and morphologic criteria for a diagnosis of tuberculosis of the skin and then study the more definite data, such as the presence of tubercle bacilli, which may be determined either directly or by inoculation of animals. One thing is certain—if it is impossible to identify the germ and attempts are made at diagnosis on the basis of histologic changes and the tuberculin test alone, there is always an element of presumption in the decision. Therefore, at least a number of positive factors must be had before a diagnosis of tuberculosis may be reached.

The condition of the Negress is classic lichenoid tuberculosis as it has been observed here in Negroes, but I do not think it should be said that all tuberculosis of the skin in the Negro assumes this form. I think, if accurate statistics were available, it would undoubtedly be found that there are many other types of tuberculosis of the skin, such as lupus vulgaris and colliquative tuberculosis, that are more frequent than these sarcoid-like conditions. More information must be amassed, and students must not be too ambitious in defining a stated type.

DR. RICHARD S. WEISS, St. Louis: Two patients in the group struck me rather forcibly: Dr. Finnerud's patient with the annular lesion on the back of the neck, which I would classify as granuloma annulare or erythema elevatum diutinum, and the Filipino with the lesion in the nose, which struck me as being like some forms of blastomycosis that I have observed. The sections of the latter lesion also suggested that condition. In the section I saw a very definite, circumscribed miliary abscess, and there was a good deal of polymorphonuclear infiltration around the rete pegs. I think further search for blastomycetes is indicated.

DR. RUBEN NOMLAND, Iowa City: The case Dr. Lawless presented was case 6 of the group I reported in the ARCHIVES (Nomland, R.: Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes, ARCH. DERMAT. & SYPH. **30**:59 [July] 1934) several years ago. In addition to the lesions Dr. Lawless demonstrated, the patient had other typical sarcoid lesions in the mucous membrane of the nose and in the larynx. When I examined her several years ago she showed no definite infiltration of the lungs. I think the case demonstrates the fact that the disease called sarcoid is a generalized, systematized disease.

DR. E. A. OLIVER: At past meetings there have been frequent discussions of the difficulty of differentiating papular sarcoid, lupus miliaris faciei and acnitis as they affect the face. Goldsmith in his recent book, in speaking of acne agminata of Crocker, stated that if one takes specimens for biopsy from different parts of the face, one is frequently likely to find different histologic pictures in the various lesions. Possibly some of the confusion in regard to these lesions may be due to this fact.

DR. FREDERICK R. SCHMIDT: I think the members are all indebted to Dr. Ormsby for presenting a case of the Schaumann syndrome, the first presented before this society. My experience is limited to one case of this type, in which the lesions took the form of lupus pernio. In most cases of Schaumann's syndrome there has been this type of lesion, and I think the value of this presentation lies in these facts: that examination of an enormous amount of postmortem material shows that the lesions are definite forms of tuberculosis cutis, and that patients with this syndrome usually show tuberculosis of the internal organs.

DR. F. E. SENEAR: I think I saw the patient Dr. Lawless showed before Dr. Nomland did—she appears to have been making the rounds. At the time I saw her there was a different picture from that presented today. There was nothing on the nose, as I recall, but on the upper part of the arm there were deep-seated nodules, one of which had broken down, leaving the scar that was present today. The patient then presented a picture of tuberculosis colliquativa, and I have no doubt now that the lesions were those of an early stage of sarcoid, although the breaking down at that time would not fit in with the ordinary conception of sarcoid.

DR. OLIVER S. ORMSBY: I wish to discuss only one aspect of the subject, and that is Schaumann's syndrome. This syndrome has been the subject of much discussion for a number of years, and its exact significance has been difficult to grasp. In Schaumann's early work he expressed the belief that a certain group of symptoms, which usually included lupus pernio, was in reality a manifestation of involvement of the glands and blood primarily and of other organs and tissues secondarily. On account of the resemblance of the condition to other lymphadenoses, he termed the symptom complex "benign lymphogranulomatosis."

The cutaneous manifestations in this symptom complex consist of some type of sarcoid, most often lupus pernio. Associated with these cutaneous changes there is adenitis, not only of the glands in the vicinity of the cutaneous lesions but of the glands in general. There is also involvement of the tonsils, which may or may not show clinical symptoms. The phalanges are the seat of an inflammatory, usually cystic, process, producing the lesions resembling spina ventosa. In addition to these areas, the liver and spleen are often invaded, and other structures may be involved. The change in the blood consists of a relative increase in the monocytes. In all the conditions I have mentioned, a tuberculoid structure could be demonstrated microscopically. Schaumann considered the disease to be of tuberculous origin and isolated the bovine type of bacillus in several of his early cases. He also reproduced tuberculosis in guinea-pigs inoculated with material from these patients.

In the early stages, the reaction to tuberculin is always negative. The progress of the condition is toward gradual absorption of the granulomatous process and finally to the development of pulmonary or other forms of active tuberculosis. In the terminal stage, therefore, the reaction to tuberculin becomes positive. Schaumann has demonstrated a tuberculoid structure in the tonsils, in the marrow of the bones and in internal organs at autopsy in patients in whom no symptoms had ever been present. He has also demonstrated the presence of the disease in the glands and in other places, without accompanying cutaneous change.

To sum up, Schaumann's syndrome usually comprises some type of sarcoid of the skin, more or less glandular involvement, cystic changes, lesions of the phalanges that resemble spina ventosa and involvement of the tonsils and some internal organs. There is also usually an increase in the monocytes in the blood. The diagnosis, therefore, aside from the cutaneous, and possibly osseous, lesions, depends largely upon the microscopic observations.

The difficulty of placing some cases in this group is illustrated by a patient who has lupus pernio of the face, lesions resembling spina ventosa on the phalanges and subcutaneous sarcoid of the arms, and who has been shown to this society three or four times over a period of twenty years. At the last presentation the lesions of the face had disappeared, leaving much deformity, and the phalanges had atrophied and contracted and were much deformed. Some of the deep sarcoid lesions on the arms had disappeared, but others had developed so that the aspect of sarcoid was still active after all these years. There has been no sign of development of a terminal tuberculosis.

DR. CLARK W. FINNERUD: The physician I presented had a history that was strongly indicative of a pulmonary tuberculous infection of some sort, dating back several years. Thorough search was made at that time, but it was impossible to prove that the bronchiectasis was a definitely tuberculous process. I think the process on the back of the neck is tuberculous, and while at present it looks clinically more like granuloma annulare or erythema elevatum diutinum, I think every one who saw the sections will agree that no section of granuloma annulare ever looked like this. I think it is some unusual form of circinate sarcoid. Dr. Oliver saw this man about a year ago, about the time I first saw him, and the lesions then were without elevation and strongly suggestive of pseudoxanthoma elasticum. Most of the findings leading to that conclusion have disappeared now.

The lesion in the nose of the Filipino, I think, is probably lupus vulgaris and not sarcoid. I agree with Dr. Michelson that it is impossible in the light of present knowledge to classify these lesions accurately from a clinical stand-

point, but in these two instances this diagnosis is as close as I can come. Dr. Hamilton Montgomery saw the sections from both cases and thought the doctor's condition most likely to be sarcoid and the Filipino's lupus vulgaris.

DR. T. K. LAWLESS: I hesitated to present this patient, owing to the fact that she had gone the rounds, but I decided to present her and have the diagnosis cleared. Despite the facts that she gives no indication pathologically of tuberculosis and has a negative reaction to tuberculin, in the last five cases of pulmonary involvement that I have had, the patients all died either from influenza or pneumonia.

**Sclerodermoid Nevus.** Presented by DR. OLIVER S. ORMSBY.

B. K., a woman aged *26*, was presented before this society on Nov. 18, 1936, for diagnosis of her condition. The full record will be found published in the proceedings of that meeting in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**36**:*223* [July] 1937). Sections are again presented. Nothing has been added since the previous report.

DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: I am unable to add anything to Dr. Ormsby's presentation. I considered the diagnosis of pseudoxanthoma elasticum. I have difficulty in understanding what is meant by "nevus" when the dermatosis is manifested many years after birth. I trust Dr. Ormsby will give his concept of the word "nevus" in this sense.

DR. OLIVER S. ORMSBY: Degeneration of the connective tissue was ruled out by microscopic examination and tests. The reason for putting the condition in the group of nevi is that it started shortly after the patient was born, as all other nevoid conditions do. Since the lichenoid type of nevus will begin in early life and continue to develop until the eighteenth or twentieth year, or even later, the use of that term is justified. While most of the lesions in this case developed in later years, that does not rule out nevus, for lesions may continue to develop over a period of years in some instances. I employed the term "sclerodermoid" because there were sclerodermatous features. The patient stated that the lesions began with hardening of the skin; then "bumps" developed on the hardened areas, and then the bumps became pigmented. The skin of the face was smooth and somewhat hard, suggesting scleroderma. On the chest, the back, the arms and the wrists, where the lesions are situated, the whole area is hard, like a sclerodermatous infiltration. It is for these reasons that the name suggested today was employed. As such a condition has not been previously recorded, so far as I can find, the name suggested today, together with the clinical and histologic description, will give other observers an opportunity for comparison when similar conditions appear.

**Heavy Metal Pigmentation (Chrysocyanosis?).** Presented by DR. E. E. IRONS (by invitation), DR. OLIVER S. ORMSBY and DR. M. H. EBERT.

P. M. S., a woman, was first seen by Dr. Irons in July 1936. A peculiar change in the color of the skin began eight years ago. The patient noticed that the skin around the mouth was getting blue. She states that shortly afterward the nails began to turn purple, and the discoloration gradually developed over the entire body, being exaggerated in exposed areas.

The patient has been the subject of numerous medical examinations, and a diagnosis of Addison's disease has been discussed chiefly among her various consultants. She has had numerous surgical operations, among which were appendectomy, repair of the perineum and nephrectomy for a tuberculous kidney. Her history further reveals that she has suffered from puerperal sepsis, exophthalmic goiter, peptic ulcer, chorioretinitis, herpes zoster and other less well defined conditions. It is reported that preceding the nephrectomy tubercle bacilli were found in the urine.

The results of some of the examinations made by Dr. Irons follow: The basal metabolic rate has varied from —9 to —21 per cent. Studies of the oxygen-combining power of the blood from the upper and the lower extremities showed no deviation from normal. The blood pressure has been about normal but variable. In August 1936 the systolic pressure was 128 and the diastolic 76. One week ago the systolic pressure was 96 in the left arm and 108 in the right, while the diastolic pressure was 68 in the left arm and 74 in the right. Numerous examinations of the blood have shown a reduction in hemoglobin and the number of erythrocytes, with a comparatively normal leukocyte count. The hemoglobin content has varied from 55 to 80 per cent. The number of erythrocytes has varied from 3,600,000 to 4;820,000. In most counts, the number was well under 3,000,000. The number of leukocytes has varied from 5,800 to 8,000. The differential counts have always given results within normal limits. The temperature has been normal and oscillometric readings on the leg and the arm gave negative results.

Roentgen examination of the pleural cavity showed an old pulmonary tuberculosis with a calcified nodule in the left lung and slight arthritis of the spine; calcified areas were demonstrated in the spleen. There was no demonstrable evidence of calcification in films taken to show calcification in the adrenals. There were some calcification of the aorta and slight hydronephrosis of the left kidney. No tubercle bacilli were found in the urine, and inoculations of animals with material from a specimen taken from the left kidney have resulted negatively. Electrocardiograms showed myocardial damage. Chemical examination of the blood showed no particular changes.

The chief changes in the skin at present are on exposed areas: the face, especially the nose and forehead, the sides of the neck, the dorsa of the hands and the forearms. The color is ashy gray. While the change in color resembles to a mild degree the changes in color seen in Addison's disease and also in argyria, it differs from those in both conditions but has a close resemblance to those in chrysocyanosis.

Histologic study showed a mild perivascular inflammatory infiltrate in the upper third of the corium, made up of lymphocytes, plasma cells and an occasional polymorphonuclear leukocyte. The most striking thing about the section was the deposit of pigment in the form of extremely fine black granules. These were seen in the macrophages, in a linear arrangement along the collagen fibers and in the basement membrane of the sweat glands and the sebaceous glands. The chemical reactions of this pigment were not those of melanin or hemosiderin. It did not become decolorized when exposed to Stillian's solution (6 per cent sodium thiosulfate and 1 per cent potassium ferrocyanide) for twenty-four hours. The spectroscopic examination in one laboratory showed no gold.

### Discussion

Dr. Lester M. Wieder, Milwaukee: I suggested the possibility that bismuth was responsible for this pigmentation partially because the woman had had gastrointestinal disease in the past and may have been given bismuth. Several of the other members made the same suggestion.

Dr. James H. Mitchell: I should like to ask if the sections have been examined with dark field illumination.

Dr. Theodore Cornbleet: I should like to ask how the question of infiltration of silver was ruled out.

Dr. Richard S. Weiss, St. Louis: Is it not rather easy to identify these metals in the skin by spectroscopic methods? It has been possible to identify silver, gold and nickel with the spectroscope, and I imagine the matter could be settled by spectroscopic and spectrographic methods.

Dr. Oliver S. Ormsby: There are one or two things I might add. In the first place, in the history it was stated that the woman had a gastric ulcer. One might presuppose that she took silver nitrate over a period of time, but the diagnosis of gastric ulcer was made by Dr. B. W. Sippy, and his treatment alone was employed, with no silver nitrate. Inquiries have been made at the various

hospitals and sanatoriums concerning the use of gold preparations in the management of the patient's tuberculosis, but no evidence has been found that any was employed.

In cases of pigmentation due to gold the gold has been found deposited in the skin in areas where light comes in contact with the skin. In this case sections from the thigh, where there was no pigmentation, showed no heavy metal, but the metal was abundantly present in sections taken from the side of the neck, where pigmentation was evident.

NOTE.—After the meeting in January a report on spectroscopic examination of fresh tissue, made by Dr. Gordon H. Scott, of Washington University (St. Louis), stated that silver was present in considerable quantities. There was no gold, bismuth or mercury.

**Melanoma Treated with Radium.** Presented by DR. OLIVER S. ORMSBY.

S. S., a woman aged 38, was presented before this society at the meeting in December 1936. The full record will be found in the report of the proceedings of that meeting in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**36**:233 [July] 1937).

Photographs illustrating the condition before treatment were presented at that time.

DISCUSSION

DR. L. F. WEBER: This certainly is a brilliant result. I have one question: What is the benefit of all the heavy filtration in the use of radium and of the long exposure? What is gained in the treatment?

DR. JAMES R. DRIVER, Cleveland (by invitation): While the technic used in irradiation here is somewhat different from that usually employed, this case illustrates the possibilities of irradiation in the treatment of melanoma. My associates and I have treated like conditions with roentgen rays by the Coutard technic. Total doses as high as 10,000 roentgens are given over a period of two or three weeks. Individual doses of from 400 to 800 r are given daily or every other day until the required amount is received.

In the treatment of many malignant lesions of the skin this method is far superior to older technics, and thus far its possibilities have not been sufficiently appreciated by dermatologists.

I have recently seen a moving picture illustrating the use of the Chaoul apparatus by which the roentgen radiation is applied directly (contact therapy) to malignant tumors of the skin and mucous membranes. Fractional doses as prescribed by Coutard were used, and the results were convincing. This apparatus can be used in the treatment of lesions in the mouth and is advocated particularly when radium is not available.

DR. OLIVER S. ORMSBY: At the meeting in December, when I first presented this patient, the question of the exact technic of treatment was brought up, and so that was inserted in the proceedings of that meeting and read again today. The technic is probably based on the experience of the man who used the treatment, who in this case was Dr. William L. Brown. I thought the lesion was a menace and required energetic treatment; so the patient was referred to Dr. Brown.

**Paget's Disease of the Right Breast.** Presented by DR. JAMES H. MITCHELL.

This woman, aged 45, presents a disease of five years' duration. It began about the nipple and gradually enlarged. She received no medical attention except home remedies until she came under observation on Sept. 21, 1936. She experienced no pain or discomfort, except soiling of her clothing by a serous discharge. She is very emotional and fears the worst but will not submit to any operative procedure. She has never been pregnant.

When the patient was first seen there was a sharply defined lesion, 11 by 14 cm., centered about the right nipple, which was palpable but not visible.

The left nipple was completely flat. Neither nipple has ever been prominent. A few firm masses were palpable in each breast, those in the right breast being no larger than those in the left. Large ulcerated areas were present about the nipple. A small gland was noted in the right axilla.

Treatment consisted of 2,100 r, unfiltered, to the lesion and 350 r, filtered through 1 mm. aluminum, to the gland in the axilla. The gland has undergone complete involution, suggesting the probability that the involvement was not a metastasis.

### Discussion

Dr. Louis A. Brunsting, Rochester, Minn.: A biopsy will be necessary in this case, in order to substantiate the diagnosis. In Paget's disease I think the treatment of choice is radical excision of the breast, for in a high percentage of cases it has been shown that there is also carcinoma of the ducts and possibly also of the adjacent glands in the axilla. It is Broder's opinion that in such instances there are three distinct types of carcinoma, not necessarily related to each other.

Dr. Richard S. Weiss, St. Louis: I agree with Dr. Brunsting. A number of cases like this come under observation at the Barnard Free Skin and Cancer Hospital, and it is the feeling there that the radical operation is indicated in every one, with dissection of all the regional glands. I am sure Dr. Mitchell has some reason for not using that type of treatment.

Dr. Theodore Cornbleet: I had a patient with an eczematoid eruption of the nipple, for which she received some radiotherapy. The external lesions healed entirely on the nipple, but the axillary glands enlarged, and microscopic sections of them showed adenosarcoma. The entire breast and the glands were resected.

Dr. E. A. Oliver: Conditions of this type, I believe, should all be treated surgically. Within the past year a woman with Paget's disease was referred to me by a surgeon for radiotherapy. After the first course of treatment the disease appeared to be cured. Recurrence, however, took place within six months, and radical removal of the breast and gland was performed. Carcinoma of the breast was found at the time of operation.

Dr. Chester A. Doty, Detroit (by invitation): I am associated with a clinic for patients with cancer. In recent years several cases of Paget's disease have been under observation there, and treatment of both types has been employed, some patients receiving surgical and roentgen therapy after operation and some, roentgen therapy alone. At present few of these patients are alive.

Dr. M. F. Engman Jr., St. Louis (by invitation): There is one point I should like to mention regarding the diagnosis of Paget's disease of the nipple. At times one finds women with marked erectile tissue in the areola. This may simulate early Paget's disease with what appears to be considerable nodular infiltration. Patients have come to us with a diagnosis of Paget's disease made by some doctor who advised that one or both breasts be amputated. A warm wet application laid on the breast for a moment will collapse the erectile tissue, and the infiltration will disappear at once. In some cases a breast has been found to be perfectly normal and a patient has been saved by this means from a serious and unnecessary operation.

Dr. James H. Mitchell: All writers on the subject agree that amputation is the only method of treatment for Paget's disease of the nipple. However, this patient prefers death to operation, and, as the process has been going on for five years and the cutaneous lesions, at least, are at the present time healed, it would seem that death is not imminent. Radiotherapy has proved in this case to be an effective temporizing therapeutic agent. If possible, I will present the patient at the next meeting of this society.

I cannot say positively that the condition is Paget's disease, for I have no material for biopsy and shall not be able to get any.

I think the nodule in the axilla was not a metastasis, because it disappeared so promptly. The nodules in the right breast are of the same size and type as those in the left breast, and the patient assures me that they have been present since she was a young girl.

**Mycosis Fungoides.** Presented by Dr. T. K. Lawless.

J. W. S., a Negro waiter aged 61, was first seen eight months ago because of pruritus. At that time his skin was generally dry and scaling, with some evidence of lacerations due to scratching. His general health was good up to two years ago.

The cutaneous lesions consist of patches, plaques, tumors and polymorphous, infiltrated and occasionally scaly lesions, varying from a few millimeters to 4 or 5 cm. There is some tendency for circinate and serpiginous outlines to form. The lesions are edematous, and several which appeared five weeks ago are reddish brown and show ulceration.

The Wassermann and Kahn tests were negative. Examination of the urine revealed a few hyaline and granular casts and albumin (2 plus). Examination of the blood showed 4,040,000 erythrocytes, 9,550 leukocytes and 14.76 Gm. of hemoglobin per hundred cubic centimeters determined by Newcomer's method. The differential count revealed 15 per cent lymphocytes, 3 per cent large mononuclears, 78 per cent polymorphonuclears, of which 8 per cent were band cells and 70 per cent, segmented forms, and 4 per cent eosinophils. The blood pressure was 200 systolic and 120 diastolic.

Microscopic slides are presented, showing a histologic picture considered characteristic of the disease.

**Leukemia of the Skin.** Presented by Dr. Theodore Cornbleet.

B. H., a woman aged 43, entered the Cook County Hospital complaining of menstrual irregularity, a growing abdominal tumor, increasing weakness and a cutaneous rash. She was sweating almost continuously.

At her initial examination her temperature was 102 F., her pulse rate 108 and her respiratory rate 20. The blood pressure was 122 systolic and 64 diastolic. The patient was listless and pale. The accessible lymph glands were enlarged. A large, firm mass was present in the left upper quadrant of the abdomen. It reached as high as the eighth rib in the midaxillary line, 3 fingerbreadths to the right of the umbilicus and halfway from the umbilicus to the symphysis. It was not tender, and it moved on inspiration. An eruption consisting of flat follicular papules was scattered evenly over the trunk and the extremities. The papules were brownish red and on palpation gave a sense of depth. Scattered groups of petechiae also were noted. The palms and soles were not involved. There was little pruritus.

Examination of the blood on Jan. 13, 1937, showed 1,420,000 erythrocytes, 88,300 leukocytes and a color index of 1. The differential count showed 5 per cent polymorphonuclear neutrophils, 25 per cent lymphocytes, 1 per cent monocytes, 69 per cent lymphoblasts and no eosinophils or basophils. On Jan. 18, 1937, examination showed 1,170,000 erythrocytes, 32,200 leukocytes and a color index of 1.10. The differential count showed 1 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes, 89 per cent lymphoblasts and no eosinophils, basophils or monocytes. There were anisocytosis and polychromatophilia, and many macrocytes and basket cells were present.

A biopsy specimen has not been obtained.

**Lymphatic Leukemia (Chronic); Leukaemia Cutis.** Presented by Dr. Theodore Cornbleet and Dr. E. L. Murphy (by invitation).

M. N., a woman aged 65, states that cracking of the skin over the backs of her hands began six years ago. She was seen at that time by Dr. E. A. Oliver, who sent her to the Central Free Dispensary, where she received therapy with ultraviolet rays. This treatment brought some relief. Since that time various areas of the body have been involved, and as each healed new areas became involved. One year ago the skin over the lateral surface of the right forearm became involved with an infiltrative process, which resembled a lichen simplex chronicus and was pruritic. At about the same time the vulva was affected with a similar process, associated with marked pruritus, for relief of which the patient came to the dermatologic clinic at the Cook County Hospital.

Two years ago a cold developed, and the physician who attended the patient after examining her blood, told her she had too many leukocytes. Since then the only symptoms she has noticed have been weakness, which is noted after she has been up and around for several hours, and some dyspnea. One year ago the right eye became involved, and examination revealed a blocked lacrimal duct.

Physical examination revealed only a few palpable lymphatic glands. The spleen was not palpable, and the heart and lungs showed no abnormality.

Laboratory findings: The Wassermann test gave a negative result. Examination of the blood showed 4,830,000 erythrocytes, 53,450 leukocytes and 98 per cent hemoglobin. The differential count showed neutrophils, 12 per cent; lymphocytes, 86 per cent, and young lymphocytes, 2 per cent. The urine was acid but otherwise normal.

A biopsy was reported on as follows: The epidermis showed acanthosis and fusion of the rete pegs. There were sharply circumscribed mantles of densely packed lymphocytes about the blood vessels in the upper part of the corium, and many small and large lymphocytes were present within the papillae.

DISCUSSION

Dr. Louis A. Brunsting, Rochester, Minn.: The widespread eruption of urticarial papules in the women is quite typical of leukemid or true leukemic infiltration in the skin.

In making smears of blood for special examination for immature cells, it is better that a specimen be taken from the lobe of the ear than from the tip of the finger. Dr. F. J. Heck has cited instances to me in which the leukocyte count from the tip of the finger was 3,800, while in the same person the leukocytes from the lobe of the ear numbered as high as 90,000. Immature cells and other abnormal types can be detected earlier and more easily in blood from the lobe of the ear than in that from the tip of the finger.

Dr. E. A. Oliver: About three years ago I presented a Negro with mycosis fungoides. At that time I had occasion to consult the literature as to the frequency of the disease among Negroes. As I recall it, the disease is not often seen in members of that race.

Dr. M. H. Ebert: About two years ago I showed before the society a Negro with extensive mycosis fungoides, not as extensive as in the case of Dr. Lawless' patient, but fairly well developed. In that case arsenical therapy was used internally to toleration, and roentgen therapy was administered to the lesions. The man was in excellent shape when I saw him three months ago.

Dr. A. B. Loveman, Louisville, Ky. (by invitation): Regarding the relative frequency of the disease in Negroes and in white persons, in the last few years in Louisville I believe there have been nearly as many cases of lymphoblastoma in Negroes as in white persons.

Dr. Frederick R. Schmidt: My impression of the lesion in the case shown by Dr. Cornbleet was that it was a small papule. If I am wrong I wish to be corrected.

Dr. Paul A. O'Leary, Rochester, Minn.: Both women presented by Dr. Cornbleet had equally high blood counts; yet not only their clinical pictures but their prognoses are quite different. The woman with the papular lesions has a comparatively short life expectancy, whereas the woman with the plaques has a much longer life expectancy. The quantity of the lymphocytosis is of decidedly less significance than the quality; hence, I believe detailed cytologic study is essential to prognosis in cases of this type.

Dr. H. E. Michelson, Minneapolis: I agree with Dr. O'Leary that sometimes there are patients with leukemia whose general condition continues to become worse even though the blood count remains stationary or even improves.

Dr. Theodore Cornbleet: I have not taken a biopsy specimen from my first patient as yet, but I anticipate that I shall find some infiltration when I do. It is

interesting that she has had no pruritus—at least, since I have been observing her. The second patient also has little pruritus, and she has a specific infiltrate. My impression is that when a specific infiltrate is present there is usually less pruritus than there is when the infiltrate is nonspecific.

**Syringocystadenoma.** Presented by DR. OTTO H. FOERSTER, Milwaukee, DR. H. R. FOERSTER, Milwaukee, and DR. LESTER M. WIEDER, Milwaukee.

E. H., a man aged 37, observed the first lesions of his eruption eighteen or nineteen years ago. All the lesions now present made their appearance during the first six months, marked changes following their initial development. At times faint scaling has been noted on mild rubbing of the lesions, but no other secondary changes have been noted. There have never been associated symptoms of any kind. There is no history of other cutaneous diseases, including urticaria. No response has been observed to various ointments or to the use of roentgen therapy, concerning the dosage of which information is not available.

Involving the clavicular areas, the adjacent upper parts of the shoulders, the upper part of the interscapular and lumbosacral regions, the flanks, the abdomen and the folds of both groins is a monomorphous discrete papular eruption composed of lesions with rounded surfaces and varying in size from that of a glass pinhead to that of a small pea. The lesions show pigmentation varying from light buff to sepia. On palpation they are found to be of soft fibrous consistency, and rubbing produces faint branny scaling over the larger lesions but no urtication. Pigmentation is noted only in association with the papulation.

Microscopic examination of a lesion removed from the flank showed little change in the epidermis except rather dense hyperpigmentation of the basal cell layer. This increase in pigment was practically confined to the tips and adjacent sides of the rete pegs, that part of the basal layer capping the papillae showing little change. There was likewise a moderate increase in the chromatophores of the subjacent dermis. The pars papillaris and the pars subpapillaris showed no remarkable change, but in the pars reticularis there was a large group of dilated cystic coil glands of various sizes, many with typical "tails" of epithelial cells attached. The ducts were lined with single, or in places double, layers of cells, and the lumens in many instances were filled with colloid material. Short strands of epithelial cells were seen lying free in the dermis between the ductlike structures.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City: I think this patient presents typical widespread syringoma, with lesions on the trunk and the eyelids. These lesions usually develop at puberty and increase in number and amount of pigment as the patient grows older. I think this type must be differentiated from the type of syringoma that involves the eyelids alone and occurs in women at or about the menopause.

DR. DAVID LIEBERTHAL: Has this patient been given any treatment? If not, I advise using roentgen therapy. In every case in which I have used that type of treatment the condition has absolutely cleared up. In regard to the remark of Dr. Nomland, in the majority of instances syringoma of the eyelids occurs in women, but there are many exceptions. I observed two cases of syringoma of the eyelids, in a mother and a son. The lesions developed in the mother at about the age Dr. Nomland mentioned, but in the son the first signs were noticed when he was about 18.

DR. OLIVER S. ORMSBY: I think it is a question of terms. Ordinarily a condition such as that in the case presented today would be classified as syringocystadenoma, a term which is synonymous with syringocytoma. The condition is different from syringoma. In the last-named condition the lesions may be generalized. In a case I observed several years ago there were large numbers of nodules of various sizes on the face, lids, forehead, trunk and extremities. They were pale red to brown or colorless and varied in size from less than that of a split pea to that of a coffee bean. During the height of the process the patient

did not perspire. An effort was made to get some sweat for chemical examination, but it was impossible to induce perspiration. With serial sections it appeared evident that the epithelial proliferation came from the sweat glands. The patient was treated with roentgen therapy for two years, and the lesions cleared up. After the lesions had disappeared, perspiration became normal. Syringoma is quite distinct from syringocystadenoma or syringocystoma.

DR. S. W. BECKER: It would appear from the single section presented that the epithelium is abnormal, in that the rete processes are long and slender and are often united at their distal ends. It would be interesting to examine a section not involved by one of these tumors, to see whether this abnormality prevails over the entire body or whether it appears only in the diseased area.

DR. LESTER M. WIEDER, Milwaukee: We saw this patient only once before he came to the meeting; so our information is rather limited. He did have roentgen therapy some years ago, and no appreciable effect followed, so far as he could observe, but we do not know the dosage or the technic employed. He also had what was probably arsenical medication some sixteen or seventeen years ago, and we thought this might account for the unusual pigmentation in some of the lesions. In the textbooks pigmentation is mentioned in the clinical descriptions, but little or nothing is said about pigmentation in the description of microscopic changes. We were surprised to see the amount of pigment in these sections. The textbooks likewise state that roentgen therapy is useful, but none describes a proper dosage.

**Keratoderma Climactericum (Haxthausen).** Presented by DR. S. W. BECKER and DR. M. E. OBERMAYER.

M. M., a Turkish-born housewife aged 59, first complained of her present trouble during the summer of 1936, when there were erythema and fissuring of the palms. Several weeks later she noted discrete areas of hyperkeratosis on the palms, and two months later a similar condition appeared on the soles and the plantar surfaces of the toes. This progressed slowly until the dorsal surfaces of the first and second toes were involved. There were mild subjective symptoms of burning and pruritus. During the last several months the condition has remained stationary.

The past history is irrelevant. Menopause occurred at the age of 50. There is no family history of a similar disease.

Physical examination showed no findings of importance except for moderate obesity. Blood pressure was 140 systolic and 90 diastolic. The reactions to Kolmer and Kahn tests were negative, and the urine showed many leukocytes. The uric acid content of the blood was 3.1 mg. per hundred cubic centimeters.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Haxthausen described the syndrome which he called keratoderma climactericum, consisting of symmetrical lesions and keratosis of the palms and soles in obese adults of middle or advanced age, most of whom have hypertension. In a discussion of such cases Barber mentioned the fact that the level of uric acid in the blood is frequently elevated. I have observed a number of cases in which the condition fitted this description, but not all the features were discernible in each. Sometimes there were plaques of dermatitis elsewhere as well—around the ears, the neck, the groin and the flexural folds of the extremities—and there frequently was a background of hypersensitivity otherwise. In this case of Dr. Becker's the keratoses are very prominent, especially on the feet, but these are not of the punctate type. I think the process may be regarded as a form of squamous neurodermatitis or, rather, symmetrical lichenified neurodermatitis with hyperkeratosis involving the palms and soles particularly.

DR. M. F. ENGMAN JR., St. Louis (by invitation): Dr. Engman Sr. in lectures to medical students and at meetings has discussed a syndrome of hypothyroidism, but he has never published his findings. This syndrome may include

the usual general hypothyroid symptoms to a greater or less degree, but in particular there is a chronic hyperkeratotic eczema of the palms and soles which is usually characteristic. It appears at the points of greatest trauma in these areas and is sharply outlined, moderately inflamed and markedly hyperkeratotic.

The syndrome described by Haxthausen in the *British Journal of Dermatology* (**46**:161 [April] 1934) may well be a description of this disease, as hypothyroidism may occur at the time of the menopause. The observations on Dr. Becker's patient seem to conform rather well to that description, and I suggest that studies of the thyroid, including determination of the basal metabolic rate and the cholesterol content of the blood, be made. In such cases the basal metabolism is usually low and there are other signs of hypothyroidism; however, there may be a normal or even a plus basal metabolic rate. Apparently the cutaneous hormones elaborated by the thyroid may be deficient, even though the hormones governing metabolism may be normal or increased. Thyroid medication has usually given splendid results in my cases.

DR. RICHARD S. WEISS, St. Louis: I wish to corroborate what Dr. Engman Jr. has just said and add that the basal metabolic rate is not an entirely trustworthy criterion of the existence of this condition. I have seen keratoderma on the palms and soles and at points of trauma, have found basal metabolic rates varying from + 5 to — 15 per cent, which is not a great deviation from the normal, and have given thyroid extract with definitely good results. Recently it has been shown that there is another indication of hypo-activity of the thyroid gland, and that is the cholesterol content of the blood. In a number of cases which had been classified as instances of subthyroid states and in which the metabolic rate was practically within normal limits values for the cholesterol content of the blood were found to range as high as 300 or 350 mg. per hundred cubic centimeters, and administration of thyroid extract has reduced this figure to 150 or 160 mg., while the skin has improved definitely with this treatment. Thyroid treatment also causes improvement in certain cases of dermatitis on the face, the neck and the chest that cannot be attributed to any contact and which has frequently been associated with hypothyroidism, with a basal metabolic rate not far from normal. Now it is found that a high cholesterol content of the blood is an indication of hypothyroidism. The doses of thyroid extract can be increased to 5 or 6 grains (from 0.325 to 0.39 Gm.) a day in many instances with good results.

DR. S. W. BECKER: I appreciate the discussion. We may have seen patients with the same type of involvement before, but if we did we called it neurodermatitis. At the annual meeting of the American Medical Association in Cleveland, Drs. Cole and Driver presented a condition identical with this (ARCH. DERMAT. & SYPH. **31**:721 [May] 1935), and the article of Haxthausen was reviewed. The condition in these cases certainly corresponds to that described in Haxthausen's original article. We shall be glad to study the patient further to see what we can find.

**A Case for Diagnosis (Dermatomyositis?).** Presented by DR. THEODORE CORNBLEET and DR. E. L. MURPHY (by invitation).

C. B., a girl aged 6 years, was admitted to the children's ward of the Cook County Hospital on Dec. 16, 1936, because of aches and pains in all joints and edema of the lower extremities of two months' duration. The patient had been perfectly well until two months before, when she began to complain of pain in the legs while walking. She became fretful and dragged the legs instead of lifting them. The skin over the lower extremities became purplish red, particularly over the knees. Shortly before her admittance to the hospital her mother noticed swelling over the abdomen, the spine and the lower extremities. The pains in the joints were migratory, beginning in the ankles and then involving the knees. The edema was noted afterward.

The history revealed that the child was vaccinated in 1933. She had whooping cough in that year, diphtheria in 1934 and measles in 1935. There had been no recent known exposure to contagion.

Physical examination on entry showed the child to be acutely ill. Her throat was moderately injected. The heart seemed slightly enlarged on percussion. The abdominal wall was edematous, preventing palpation of the viscera, and it pitted with difficulty. There was swelling about all joints of the extremities, with pain on attempts at motion and marked pitting edema. The skin over the legs was purplish red and glistened about the knees. Pitting edema was present all over the back. There were scattered petechiae on the chest.

The blood pressure on December 18 was 134 systolic and 88 diastolic and on December 24 was 124 systolic and 70 diastolic. A diagnosis of nephritis was first considered.

Examination of the urine showed a specific gravity of 1.005, an acid reaction, no albumin or sugar, occasional pus cells and no casts.

On December 29 a smear from the throat was 4 plus for Streptococcus haemolyticus.

The Wassermann test of the blood gave negative results. Chemical studies of the blood showed 17.5 mg. of urea nitrogen per hundred cubic centimeters and a protein content in the serum of 5.92 per cent. Examination of the blood revealed 3,550,000 erythrocytes, 10,900 leukocytes and 61 per cent hemoglobin. A differential count showed polymorphonuclear neutrophils, 68 per cent; lymphocytes, 21 per cent, and monocytes, 11 per cent.

A roentgenogram of the nasal sinuses showed no abnormality.

On December 29 a Weltmann reaction of 3 — ruled out subacute bacterial endocarditis (Dr. Klein).

On Jan. 4, 1937, a biopsy specimen of skin, subcutaneous tissue and muscle (gastrocnemius) was submitted for examination. On January 17 Dr. Richard H. Jaffé reported a diagnosis compatible with dermatomyositis.

The histologic picture showed patches of muscular fiber and dense connective tissue. In the interstitial tissue of the bundles of muscle and in the dense connective tissue about the blood vessels there were dense accumulations of large mononuclear cells with slightly irregular and kidney-shaped nuclei.

### DISCUSSION

Dr. Paul A. O'Leary, Rochester, Minn.: It is difficult to make the diagnosis of dermatomyositis in the early phase of the disease because it is frequently impossible to distinguish acute dermatomyositis from sclerema adultorum, acute edematous scleroderma and acute trichinosis. The study of a biopsy specimen taken from the muscle during the acute stage of dermatomyositis does not settle the diagnosis, for the characteristic muscular changes are late manifestations of the disease. A biopsy specimen from a muscle taken shortly after the onset of the disease showed an acute inflammatory reaction which was not diagnostic. The child presented by Dr. Cornbleet presents the clinical picture which it has been customary to diagnose as dermatomyositis, but I believe further observation, perhaps for several months, will be necessary in order to confirm this diagnosis. Owing to the short duration of the disease in this patient it would seem advisable to institute nonspecific therapy at once in the form of typhoid vaccination or fever therapy and administration of amino-acetic acid. Within the last three weeks I have seen again the three patients whom my associates and I showed at the meeting of the Dermatological Conference of the Mississippi Valley last fall (Arch. Dermat. & Syph. **35**:985 [May] 1937). The adult is walking about freely and has improved markedly. The two children have shown no improvement.

In the taking of a specimen for biopsy from a muscle care should be exercised in the selection of the muscle to be studied. The group of muscles in the shoulder are most frequently involved, and the degenerative changes there are manifested early, while the muscles of the calf are involved late and only when the condition is extensive.

Dr. Ruben Nomland, Iowa City: I have had under observation a child with dermatomyositis of from six to eight months' duration. I have seen the child in

conjunction with the pediatric department. Dr. P. C. Jeans, of the pediatric department, conducts a metabolic clinic, and one of the points of interest in the case is that the child shows a greatly decreased output of creatinine, which to Dr. Jeans indicates a marked loss of muscle volume. Dermatomyositis leads to destruction of the muscular tissue, with a decrease in the output of creatinine in proportion to the destruction of muscle.

DR. THEODORE CORNBLEET: I agree that further observation is necessary to justify a diagnosis of dermatomycosis. I think the condition here is one which fits into a group of diseases which are all fundamentally related. In this there is an infection or toxemia that injures the muscle and the skin, and the changes resulting may be reversible. After the primary injury to the tissue, secondary changes may take place, such as those, for instance, which occur in scleroderma, where varying amounts of calcium may be deposited.

**Progressive Pigmentary Dermatosis (Schamberg's Disease).** Presented by DR. A. W. STILLIANS and DR. E. M. SMITH JR. (by invitation).

C. D. R., a man aged 31, was first seen in May 1929, when he complained of red spots and pigmentation of both ankles, involving the medial and lateral surfaces below the malleoli and also the dorsa of the toes. The lesions appeared as pinhead-sized bright red macules which slowly became darker. At that time the patient also complained of a recurrent vesicular eruption of both palms, examination of which revealed no fungi and which persisted until November 1929. In April 1930 examination by a capillary microscope showed dilated capillaries overlying a deeper or much finer angioma, a network radiating like a spider nevus. The vessels were fine. On the pigmented or confluent red spots little could be made out.

The patient returned in November 1936 with one recently healed ulcer and a second ulcer on the right ankle. This lesion was covered by a heavy pellicle, on removal of which several skin-covered areas were noted.

Laboratory reports showed no abnormality.

Biopsy was performed in 1930 to rule out Kaposi's sarcoma. No evidence of this disease was found. Since then ill defined fairly firm papules from 0.5 to 0.7 cm. in diameter have appeared on the tops of the distal phalanges of several toes. Both sides of the ankles are covered with dark brown pigment, along the borders of which are groups of cayenne pepper telangiectases. On the inner side these extend along the side of the foot halfway to the toes. On the inner side of the left ankle are three small scars, the sites of former ulcers. One similar scar is present on the inner side of the right ankle.

On the dorsa of all the toes the same type of pigmentation extends a few millimeters beyond the base of the toes, with scattered telangiectases.

An effort will be made to excise one of the papules for microscopic study.

**A Case for Diagnosis (Stomatitis Exfoliativa?).** Presented by DR. W. M. WILLETT (by invitation) for DR. S. W. BECKER and DR. M. E. OBERMAYER.

M. K., a woman aged 32, a housewife, was first seen in a medical clinic in September 1936, complaining of nausea associated with loss of appetite and insomnia of about one year's duration.

The general physical examination and clinical determinations in the laboratory showed no abnormality, except for some grayish white patches distributed over the buccal mucosa and hard and soft palates. As far as the patient is aware, this condition has been present all her life. She associates exacerbations of the condition with the attacks of nausea which occur at intervals of from two to four nights. About twelve years ago she was subject to epileptic seizures. During that time she took bromides, and she states that the oral condition cleared up for a period of at least one year. She does not recall, however, when the condition reappeared.

On the patient's first visit an examination was made for Monilia, and the result was thought to be positive. For this reason the patient was given a 2 per cent

aqueous solution of methylrosaniline to apply locally. After two weeks' treatment there was no change in the condition. Repeated examinations for Monilia have given negative results, and the patient has discontinued the treatment. An interesting fact is that her father has had a similar, if not identical, condition of the oral mucous membrane for many years.

Biopsy showed the epithelium to be thickened to four times its normal thickness. The most superficial portion was fairly dense. The cells were flattened and contained pyknotic nuclei. Beneath this and extending almost to the basal layer the cells were loosely held together and vacuolated. There was both intercellular and intracellular edema with a little typical spongiosis. The basal portion of the epithelium appeared normal, and the connective tissue showed only slight if any cellular infiltrate. Gram's stain showed no fungi or spores and only an occasional organism.

DISCUSSION

Dr. Otto H. Foerster, Milwaukee: The question has been raised as to whether the condition in this case is mycotic or whether it is lichen planus. I thought that the extent and location of involvement of the mucosa and the absence of striate lesions with internodal thickenings were points against the diagnosis of lichen planus, while the peculiar tufted appearance of the tongue, more pearly than whitish, and particularly the membranous character of the lesions in the gingivobuccal folds would favor a diagnosis of thrush. The history of a similar condition said to be present in another member of the family might give support to this diagnosis.

Dr. Paul A. O'Leary, Rochester, Minn.: I felt as Dr. Foerster did, that the patient presented a monilial infection of the mouth called submucous thrush. However, for several years Dr. G. B. New and I have been trying to determine just what is meant by this term. We have been examining patients with conditions of this type for evidence of lichen planus and in addition have done biopsies on these lesions of the mucous membrane in an effort to distinguish between submucous thrush and lichen planus. It is true that it is most difficult to demonstrate Monilia albicans, and when it is found some question is raised as to its pathogenicity. Examination of the vaginal tract often shows the same involvement. This patient says she has no such involvement, but examination might prove the presence of lesions similar to those in the mouth, as the disease is frequently asymptomatic in the vagina.

Dr. Theodore Cornbleet: Last year I presented before the society a man in whom an identical condition was present. He showed in addition perlèche and bolster rolls about all the nails. M. albicans grew on culture of specimens from below the folds of the nails. In spite of the variety of lesions supposedly due to Monilia and the actual presence of the latter in some of them, it was impossible to isolate these fungi from the oral lesions after repeated efforts.

Dr. Richard S. Weiss, St. Louis: In my experience monilial infections of the mouth do not give the appearance present on the lips in this patient, but the condition is similar to lichen planus. I think this condition may prove to be lichen planus.

Dr. M. E. Obermayer: In searching the books and papers on this subject I came on a thesis in the new Arzt-Zieler handbook (Arzt, L., and Zieler, K.: Die Haut- und Geschlechtskrankheiten, Berlin, Urban & Schwarzenburg, 1934, vol. 3, p. 128), in which pseudothrush is mentioned. It is stated that Grasset described this disease. We thought the term pseudothrush fitted this clinical entity. I wonder whether any of the members has ever heard of the paper by Grasset describing pseudothrush.

Dr. S. W. Becker: When the patient was first seen we thought the condition was thrush, but repeated examinations gave negative results. I know the work of Dr. New, which Dr. O'Leary mentioned, has been carried on for several years. and the organism has been observed on sectioning when it could not be demon-

strated on scraping. In this case the section did not show lichen planus but revealed exfoliation of the mucosa. Gram stains showed a few bacilli but not enough to account for the exfoliation, and thrush was not revealed.

**Morphea.** Presented by DR. E. A. OLIVER.

M. L., a woman aged 52, a housewife, was seen on one occasion five years ago with an erythematous eruption over the thighs and abdomen, which was thought to be erythema multiforme. Where this eruption formerly was located, the patient now presents infiltrated pale areas surrounded by violaceous halos. The skin is smooth, rather shiny and stiff in these areas.

A biopsy was presented.

DISCUSSION

DR. RICHARD S. WEISS, St. Louis: I suggest a diagnosis of morphea.

**A Case for Diagnosis (Elephantiasis?).** Presented by DR. E. A. OLIVER, DR. F. J. KENDRICK, Gary, Ind., and DR. RALPH H. SCULL (by invitation).

V. N., a man aged 18, was born in Pennsylvania and moved to Gary, Ind., seventeen years ago. He has lived nowhere else and has not had any contact with any foreign country. His history has been difficult to obtain in detail, and records from previous admissions to hospitals have been of little assistance.

Briefly, he had a generalized cutaneous eruption, which was called exfoliative dermatitis, from 1925 to 1930, and this was punctuated by sharp febrile periods lasting several days. During that time a lateral curvature of the spine developed, and about 1928 the external genitalia began to enlarge. A paroxysm of fever (104 F.), accompanied by chills and sweating and lasting for twenty-four hours, was observed about a month ago. This attack was accompanied by an erythematous eruption of the right side of the chest, which gradually faded, with exfoliation. Similar attacks have occurred at infrequent intervals since their first appearance.

Filarias have been sought in the blood stream, with negative results. A week ago a spirochete, presumably of the group which cause relapsing fever, was found on dark field examination of the blood. The Wassermann test gave negative results.

DISCUSSION

DR. RUBEN NOMLAND, Iowa City: It seems to me that this man presents typical findings of lymphedema as a result of streptococcic infection. I do not believe the finding of the spirochete would be anything more than incidental, or perhaps an artefact was mistaken for a spirochete.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This patient presents moderately advanced lymphedema or elephantiasis of the region of the genitalia, which is the result of repeated bouts of what is, presumably, an erysipelatous or streptococcic infection. The same picture may appear on the nose, the ear or the digits, but particularly on the feet and wherever the circulatory return may be impeded. Treatment by means of filtered roentgen rays and various types of vaccine may be of some help in the prevention of subsequent attacks. When the lymphedema is well established, however, little can be done, except by plastic operation or, in the case of the legs, by the use of supporting bandages of rubber. The ordinary elastic supports are usually worthless in cases like this.

DR. JAMES R. DRIVER, Cleveland (by invitation): The presenter's diagnosis is probably correct. However, there are some scars in the groins which may have resulted from a previous adenitis. For this reason Frei tests should be performed. If the patient has had lymphogranuloma venereum the elephantiasis of the penis may perhaps have occurred in the same manner in which esthiomene occurs in women who have had this disease.

DR. MAX S. WIEN: The enlargement of the scrotum resulting from elephantiasis nostras may sometimes reach proportions similar to those seen in cases in

which the condition is due to filariasis. About five years ago there was a patient on the service at the Cook County Hospital whose scrotum was so enlarged that it reached to his knees. The condition was the result of an elephantiasis secondary to chronic urinary extravasation, occurring as a sequela of multiple postgonorrheal strictures, periurethral abscesses, urinary fistulas and "sprinkling-pot" perineum. A diagnosis of lymphogranuloma venereum in the case presented cannot be made without a strongly positive reaction to the Frei test. There is something about the edema in this case, however, that differs from that usually seen in the elephantiasis of lymphogranuloma venereum. The edema in that disease is more of an infiltrative tenseness, rather than the soft pitting edema seen in hypostatic conditions or the hard type of "woody" infiltration seen in phlegmonous cellulitis.

DR. PAUL A. O'LEARY, Rochester, Minn.: I have had two patients with persistent edema of the genitalia in whom plastic surgical measures have been successful not only in reducing the edema but in minimizing the frequency and severity of the febrile attacks. The technic employed was similar to that advocated by Kondoleon, as performed on patients with persistent or solid edema of the extremities. It has been shown that the edema itself becomes a prominent factor in precipitating the recurrent attacks, so that the patient enters a vicious circle, as it were, the edema predisposing to the recurrent attacks of lymphangitis with fever, which in turn produce further lymphatic obstruction and edema. In the lower extremities the use of bandages made from heavy rubber helps materially to keep the edema down. In patients such as this one, however, such a procedure is hardly practical, and surgical measures have been attempted in an effort to reestablish the lymphatic circulation without using the bandage as a means of reducing the solid edema. Thus far, the results have been most encouraging, in that the attacks of lymphangitis are less severe and less frequent, although some deformity persists. Typhoid vaccine has been given postoperatively for its nonspecific benefits.

**A Case for Diagnosis (Scrofuloderma?).** Presented by DR. JAMES H. MITCHELL and DR. W. W. TOBIN (by invitation).

This man, aged 45, was first seen one year ago, when he complained of "running sores" on the right side of his chest, accompanied by a constant dull pain of one year's duration. He states that while working as a laborer in 1931 he received a blow on the right side, with injury to his right elbow and the right side of his chest, after which he was hospitalized for approximately two months. He had no further trouble until 1934, when a constant dull pain set in around the lower part of the right side of his chest. This was soon followed by the appearance of tender, reddened areas. A few months later abscesses formed in the reddened areas and drained continuously.

On physical examination the patient presented five bluish red lesions with linear sinuses around the lower right quadrant of the chest, extending from the ninth dorsal spine to the lower end of the sternum. The sinuses were of an indolent type, with undermined edges, and they exuded a thin yellowish discharge. Breath sounds were absent, and there was flatness to percussion over the entire lower half of the right side of the chest.

A roentgenogram of the chest showed marked clouding of the lower part of the right lung, but there were no changes in the bones. The Wassermann test gave a 4 plus reaction. Koch's old tuberculin test gave positive results with 0.1 cc. of a dilution of 1:10,000. Examination of a biopsy specimen taken from one of the sinuses revealed only chronic granulation tissue. Smears and cultures obtained from the sinuses showed no abnormality. Agglutination tests for tularemia and typhoid gave negative results. Inoculation of guinea-pigs with purulent material obtained from the sinuses resulted unsuccessfully.

Treatment with twelve weekly injections of neoarsphenamine (0.3 Gm.) and potassium iodide failed to produce any healing effect but caused a reversal of the Wassermann reaction. Treatment with Koch's old tuberculin also failed to elicit any response.

During the past three or four months tender erythematous infiltrated areas have appeared over the lower part of the anterior wall of the chest and the scrotum.

DISCUSSION

DR. H. C. WILLETT, Des Moines, Iowa (by invitation): I was interested, for I have observed a similar case of actinomycosis. I do not think this condition is that, for there were no yellowish granules in the secretion. I thought of tularemia and one or two other conditions, but I think search should be made for some organism of the yeast fungus type.

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## SAN FRANCISCO DERMATOLOGICAL SOCIETY

L. R. TAUSSIG, M.D., *President*

*Sept. 18, 1936*

JOHN M. GRAVES, M.D., *Secretary*

**Coccidioidal Granuloma Confined to the Tongue.** Presented by DR. HARRY E. ALDERSON.

A. J. L., a married man aged 39, a truck driver residing in Watsonville, Calif., had macroglossia of enormous proportions of six months' duration on April 14, 1936. There were two irregular superficial ulcers near the right border of the tongue, where the disease had its onset.

The patient bit his tongue in November 1935, and it has never healed. The swelling has gradually increased, and the tongue now almost fills his mouth. This swelling is fairly uniform and firm, but the borders are deeply indented by pressure of the teeth. The base of the tongue is free, but the surface in front of it shows deep-seated but slightly elevated irregular and poorly defined hard nodules.

There was never any interference with breathing, but the patient has great difficulty in eating and talking. The cervical nodes and submaxillary glands have become swollen during the last few weeks, but they do not interfere with free movements of the neck. The epitrochlear nodes are slightly enlarged.

The general physical condition is excellent. The patient has been able to continue his work as a truck driver uninterruptedly.

The Wassermann reaction of the blood was negative in January and in March. On April 16, 1936, it was negative, but the Kahn reaction was weakly positive. Physical examination revealed nothing but the conditions already mentioned.

There is no history of syphilis or gonorrhea. The patient's health has been excellent.

Carcinoma, actinomycosis, syphilis and tuberculosis were suspected. A biopsy specimen was obtained from deep layers of the skin, and the histologic examination gave results as follows: The gross specimen consisted of three small fragments of soft white tissue, the largest measuring 0.4 by 0.4 by 0.1 cm. The microscopic sections showed a piece of tongue partially covered by thickened, hyperplastic squamous epithelium which showed a moderate amount of superficial keratinization. A few small abscesses were present in the mucosa. The submucosa showed a marked granulomatous reaction, with numerous cellular tubercles composed of epithelial and large mononucleated giant cells. A rather intense inflammatory reaction was present. Contained within some of the giant cells and tubercles were medium-sized oval bodies possessing a refractile double-contoured wall. Some contained small bits of débris; others were empty, and a few contained remnants of endo-

spores. The surrounding inflammatory cells consisted chiefly of lymphocytes, occasional plasma cells and moderate numbers of leukocytes. Myriads of eosinophils were present in some areas.

The diagnosis was coccidioidal granuloma of the tongue.

It was planned to make cultures and inoculations of animals, but the patient did not return. His physician in Watsonville was unable to do much for him, and he was next heard from in Oakland, Calif., where he consulted Dr. Alfred Siefert for roentgen therapy in May 1936. Subsequently, Dr. Siefert sent in the following report: Roentgen examinations of the chest revealed no abnormalities. I gave the patient considerable roentgen radiation directed to the tongue as well as to the swollen cervical lymph glands, and at the suggestion of Dr. Dickson he received 2 grains (0.13 Gm.) of thymol three times a day by mouth. The first result of this treatment was a marked increase of the swelling of the tongue, so marked that it became alarming. Treatment with roentgen radiation and thymol was then discontinued, and the patient was given large doses of potassium iodide by mouth.

Dr. Siefert states that he saw the patient about a week ago and was much surprised at the improvement. At that time the tongue was almost normal in size, the boardlike hardness had disappeared and the discharge of purulent material had ceased; the patient had gained 7 pounds (3.2 Kg.) and felt subjectively much improved and encouraged.

DISCUSSION

Dr. Alfred Siefert, Oakland, Calif.: The patient was referred to me by a physician in Hayward, Calif., whose advice he had sought. The notes which I made on his case are as follows:

He came to me on May 2, 1936, complaining of great swelling of the tongue and inability to move it. He dated his illness to about four months back (about February 1936) at which time, after recovering from an attack of influenza, he bit his tongue. The tongue began to swell to an unusual degree but was painless. The patient also associates the condition of his tongue with the eating of fresh fruit while the wound was still unhealed. When he presented himself to me, he had lost approximately 25 pounds (11.3 Kg.). His temperature went up to 101 F. in the evening. The tongue was strikingly swollen and of boardlike hardness. At the base there was a discharging lesion whence issued thin yellowish pus. On the dorsal surface of the tongue, farther forward, there was a firm papillomatous nodule which was at first suspected of being an epithelioma but lacked the usual firm induration. On both sides the cervical glands and the submandibular lymph glands were enlarged. Roentgen examination of the chest at this time showed no pathologic changes.

When I communicated with Dr. Alderson I was informed that he had demonstrated what were considered coccidioides.

As to treatment, I am indebted to Dr. Templeton for valuable suggestions. I thought it wise to block the cervical lymphatics by means of roentgen radiation and to attempt to bring about the breaking down of the granulomatous lesions in the tongue by production of fibrosis. At the suggestion of Dr. E. C. Dickson, of Stanford University, the patient was given thymol by mouth (Sox, H. C., and Dickson, E. C.: Experimental Therapy in Coccidioidal Granuloma, *J. A. M. A.* **106**:777 [March 7] 1936). However, the dose given, 2 grains three times a day for three days, did no good in this case; on the contrary, the tongue became so swollen that the patient experienced considerable difficulty in eating and drinking. He lost weight rapidly while that treatment was being given.

Administration of thymol was stopped, and the patient was given 75 grains (4.875 Gm.) of potassium iodide each day. In a short time there was striking improvement. The swelling of the tongue receded remarkably. The serosanguineous discharge diminished considerably; the patient's appetite improved, and he was able to sleep. Roentgen therapy to the cervical glands was kept up, and they began to become firm and shotty. The patient began to gain weight.

By July the tongue was almost normal in size, soft and freely movable. The cervical and submaxillary glands were small but still palpable. The patient had gained 15 pounds (6.8 Kg.). Roentgenograms of the chest at this time again showed no abnormalities.

On August 2 the patient had regained his normal weight, which was 175 pounds (79.4 Kg.). The tongue was still slightly swollen, and the discharge had not completely disappeared. He received further roentgen therapy and continues to take potassium iodide. The total weight gained by September 12 was 25 pounds.

The size of the tongue is now almost normal and, except for the presence of a few palpable nodules, is soft and freely movable.

DR. H. E. MILLER: On the lateroposterior surfaces of the tongue there were two or three firm nodules about as big as the end of a thumb.

Primary coccidioidal infection of the tongue has never been reported in the literature. I should assume that it would be secondary to pulmonary infection with coccidioides, just as tuberculosis of the tongue is generally secondary to pulmonary tuberculosis. I think that most dermatologists assume that primary tuberculosis of the tongue does not exist. It is known that the smooth muscle of the tongue is more resistant to infection than most other parts of the body.

I hope that Dr. Alderson can effect a complete cure. I wondered when I read the pathologic report why there was débris in some of the organisms, and why endospores were not observed. I hope that cultures and inoculations of animals will be obtained ultimately.

DR. H. J. TEMPLETON, Oakland, Calif.: When I remembered that the sections showed preponderance of plasma cells, I also wondered about the diagnosis. Some of the members may remember a young Tahitian whom I showed before this society several years ago. He had about the same clinical picture, and sections from his tongue showed the same preponderance of plasma cells. Dr. W. Ophüls made a diagnosis of plasmocytoma. Some of the visitors who saw the patient suggested that his condition might be an infection with a streptothrix.

DR. H. E. MILLER: Many of the members have thought that Dr. Templeton's case was one of lymphogranuloma venereum. If the Frei test had been in use at that time, it might have been possible to determine that point.

DR. HARRY E. ALDERSON: The double-contoured bodies in the sections from this patient were quite characteristic of coccidioides—the picture was typical. I do not know what else those forms could represent. The débris is hard to explain —it might be just an artefact. I did not see any of the cells that had discharged, that Dr. Miller mentioned.

The weak points in the diagnosis in this case are, of course, the lack of cultures and of inoculations of animals, the weakly positive Kahn reaction, and the response to potassium iodide, though the patient also received a great deal of roentgen therapy.

DR. G. V. KULCHAR: I do not think that a diagnosis of coccidioidal granuloma can be discarded because of lack of cultures. The diagnosis might be supported by inoculations of animals. I think that a diagnostic test with coccidioidin would settle the question.

**Chronic Cheilitis of the Lip with Malignant Degeneration.** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

Mr. S. C., a Chinese man aged 41 years, consulted me in June 1935, because of cheilitis involving the entire lower lip. This had been present for months. On the right half of the lip there was an indurated lesion about 1 by 1.5 cm., which clinically was an early stage of epithelioma. A biopsy showed squamous cell epithelioma. This was destroyed with electrodesiccation, and the right half of the lip was given a total of 3,000 roentgens of unfiltered radiation. This lesion has remained healed.

Nine months later (in March 1936) on the left half of the lower lip, which had received no treatment, there had developed a superficial erosion superimposed on the basic cheilitis. This was destroyed by electrodesiccation.

Although the malignant process is apparently well, I fear a repetition of the process in the chronic cheilitis for which no cause has been found.

The questions which occur to me are: Should the whole area be destroyed again with electrodesiccation? Should further radiation be given to the left half of the lip, which has received none? Or should the entire mucous membrane be excised as gynecologists excise the vulva for relief of leukoplakia?

It was discovered yesterday that this patient has diabetes mellitus.

DISCUSSION

DR. L. R. TAUSSIG: The clinical appearance suggests lupus erythematosus. I grant that a diagnosis of lupus erythematosus limited to the lip is difficult to make. I dislike to make it in the face of the previous history of epithelioma. However, I think that this diagnosis is worth considering.

DR. MERLIN MAYNARD, San José, Calif.: I think that the lesion on the left side is typical of lupus erythematosus.

DR. G. V. KULCHAR: My clinical impression is the same. It is not hard to explain why epithelioma should develop on top of lupus erythematosus. While it is not a common occurrence, it may follow radiation therapy.

DR. THOMAS J. CLARK, Oakland, Calif.: I think the suggestion of Dr. Taussig that the patient has lupus erythematosus is reasonable. In cheilitis there is inflammation of the mucous ducts which in a way correspond to inflammation of the sebaceous glands of the skin, and all types of such inflammation, from seborrhea to lupus erythematosus, may occur. Often one can see definite clinical steps. The appearance of the lesion at present suggests an inflammatory discoid type of lupus erythematosus.

In answer to Dr. Templeton's inquiry as to what to do, in lupus erythematosus the treatment is, of course, largely a "touch-me-not" type of therapy. My suggestion would be to use mild stimulation with about 80 per cent phenol and in the meantime to use astringent applications—perhaps 0.25 per cent aluminum acetate as a dressing, with possibly a little powdered alum in zinc oxide ointment. I think that if this treatment were continued a nice result might eventually be obtained. I should not favor active counterirritation of any kind.

DR. H. E. MILLER: I agree with the suggestion that the condition may be lupus erythematosus. I think that treatment with gold sodium thiosulfate would not have any effect on the lip. I certainly should hesitate to apply phenol to it. I think that superficial desiccation of the area with the subsequent formation of scar tissue would be of value.

DR. J. D. VIECELLI: Has any effort been made to protect the lip?

DR. H. J. TEMPLETON: Only by the use of hydrous wool fat.

DR. J. D. VIECELLI: I think that protection from sunlight is important.

DR. G. V. KULCHAR: Some work has been done to show that sensitivity to sunlight is reduced by the use of a gold compound. I certainly should not use roentgen radiation, because this man's tolerance for roentgen rays would be impaired. Likewise, to produce scar tissue seems to be a somewhat radical form of treatment. I suggest the use of phenyl salicylate to protect the lesion from sunlight. If epitheliomas arise, it would then be time to resort to surgical or to roentgen therapy.

**A Case for Diagnosis (Lichenoid Eruption).** Presented by DR. J. M. GRAVES.

E. T., a man aged 23, a stevedore, states that his parents and one brother and one sister are all alive and well. There is no history of familial disease.

The patient has had no serious illnesses or operations. He has been in the United States Navy. He has been feeling perfectly well and is able to do hard work without undue fatigue. About three or four months ago the eruption of which he complains appeared. It developed rapidly and has since remained practically stationary. There is no pruritus.

General physical examination gave negative results except for the cutaneous lesions. These involve the trunk, the arms, the neck and the forehead. The lesions are numerous and consist of flat-topped shiny pink papules. Many are polygonal, and some are follicular. Many lesions are umbilicated. Over the extensor aspects of the elbows the lesions are collected into large plaques. On the upper portions of the arms there is definite grouping. Lesions are numerous between the scapulae and over the back of the neck. Some appear in plaques and some are annular. Some of the lesions on the neck show atrophy. The patient has received small doses of solution of potassium arsenite for ten days, but no apparent change has resulted.

The mucous membranes are normal.

The Wassermann and the Kahn test were negative. The blood count was normal. A section is presented.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: It is with considerable hesitancy that I suggest the diagnosis of a disseminated type of granuloma annulare. The pathologic picture is that of tuberculoid. Some of the larger lesions have a certain amount of firmness on palpation.

DR. J. M. GRAVES: I wanted some help on this case. When I first saw the patient I thought the condition might be lichen planus. I was not, however, at all satisfied with that diagnosis.

DR. HARRY E. ALDERSON: There are many objections to a diagnosis of lichen planus in this case, even if one were willing to make it.

DR. J. D. VIECELLI: The possibility of lichen scrofulosus might be considered.

**A Case for Diagnosis (Scleroderma?).** Presented by DR. F. H. STIBBENS, Oakland, Calif.

Mrs. Mary R. was presented before this society in the latter part of 1931 with a diagnosis of multiple benign sarcoid of the Darier-Roussy type.

Small doses of solution of potassium arsenite caused all the lesions to disappear before June 1932.

For a period of approximately two years the patient was free from any sign of the disease except atrophy of the tissues overlying the sites of former tumors. Late in 1934 she noticed pain and thickening of the skin over the outer upper quadrant of the right buttock. This continued to increase in intensity until the present time.

During the aforementioned interval she has been in fairly good health, except for a chronic cough. Repeated examinations for tuberculosis and tuberculin tests have given negative results.

During the early part of February 1936 in a fit of despondency the patient took an overdose of solution of potassium arsenite with suicidal intent, but apparently she suffered no permanent ill effects. Examination at present shows a scleroderma-like plaque about 5 by 8 inches (12.7 by 20.32 cm.) in extent, over the right buttock and upper portion of the thigh, as stated. Smaller plaques, approximately 3 inches (7.6 cm.) in diameter, are present over the posterior crest of each ilium.

It is interesting to note that there is no involvement of any of the sites where former lesions existed.

The question now is: Are the present areas a renewal of the former disease, or has a true scleroderma developed?

DISCUSSION

DR. THOMAS J. CLARK, Oakland, Calif.: This is an interesting case from the point of view of the present condition. The woman previously had a nodulation

of the skin quite typical of sarcoid. Assuming that this was on a tuberculous basis, the condition has apparently changed to scleroderma.

I think that it is sarcoid rather than what is usually considered scleroderma.

DR. STANLEY R. TRUMAN, Oakland, Calif. (by invitation): I do not know whether my suggestion has anything to do with the cutaneous lesion, but on feeling this woman's skin I thought that she might be suffering from hypothyroidism. She is always cold; her skin and hair are dry; she is easily fatigued, and she has a tendency to constipation, which would fit in definitely with such a picture. I feel that one would be justified in studying the case from an endocrine point of view. There seems to be a tendency now to believe that endocrine conditions may have some relation to scleroderma.

DR. F. H. STIBBENS, Oakland, Calif.: Before the woman came to the clinic in 1931, she was thoroughly examined for endocrine disturbances.

**Solar Dermatitis.** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

A. J. L., aged 40, was seen at various times from 1931 to 1934 because of a dermatitis of the face, neck and hands. When he was first seen this was regarded as a contact dermatitis, but complete studies by means of patch tests gave negative results. He was studied by an allergist and also by an internist, but no help was obtained.

In May 1932 dermatitis solaris was thought of, but his urine contained no hematoporphyrin.

The patient was lost sight of in 1934, but last month he reported, stating that the dermatitis was definitely due to sunshine and that he could reproduce it at will.

At present the dermatitis involves mainly the dorsa of the hands, but it has also frequently appeared on his face and neck. It is mainly of the papular variety.

He is being studied by Dr. H. Blum, who is determining which wavelengths affect him.

DISCUSSION

DR. H. C. COE, Oakland, Calif.: I saw this patient years ago, when he had a severe dermatophytosis of the feet. I wonder if the dermatophytosis might have sensitized his skin to such an extent that he is sensitive to sunlight.

**Dermatitis Herpetiformis.** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

This patient was presented previously before this society.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: Every method of therapeutic attack suggested has been tried. The patient has been given transfusions and injections of his own blood; he has been treated with solution of potassium arsenite, tryparsamide, coagulin, iron cacodylate, chromium sulfate and huge doses of viosterol. Elimination diets and some fever therapy have also been given.

DR. MERLIN MAYNARD, San José, Calif.: Has there been any effect from any of these methods?

DR. H. J. TEMPLETON, Oakland, Calif.: I cannot say that there has been.

**Seborrheic Eczema.** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

N. H., aged 19, a student at the University of California, was first seen yesterday at the Cowell Memorial Hospital. He has an extensive peribuccal erythema with some suggestion of pigmentation, which has been present for six months. He also has considerable seborrhea of the scalp. His lips and mouth have never been involved.

Although he is presented with the diagnosis of seborrheic eczema, the following questions come to mind: 1. Should a diagnosis of *érythrose peribuccale pigmentaire* of Brocq be considered? 2. Is Brocq's disease merely a manifestation of seborrhea?

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: Brocq described a peribuccal condition that looked like seborrheids and that was associated with pigmentation. I am not sure that this patient's condition is *érythrose peribuccale pigmentaire* of Brocq or just what relationship seborrheic eczema bears to his entity.

DR. HARRY E. ALDERSON: In the Hawaiian Islands I have observed cases of dermatitis venenata surrounding the mouth from eating mangoes. This patient's condition may be due to some sensitization.

DR. H. J. TEMPLETON, Oakland, Calif.: His lips are free from lesions. I thought of that also.

**Pyoderma of Pseudoblastomycetic Type.** Presented by DR. G. V. KULCHAR.

J. G., aged 27, a laborer, says that the present trouble began seven years ago as furuncles over the nape of the neck. These underwent involution, leaving keloidal scars. Soon after, there developed over the angles of the jaw, over both scapular regions and over the buttock hypertrophic infiltrated red granulomatous lesions with sinuses discharging pus. The lesions have persisted. There are no constitutional symptoms. The past history is unimportant.

Roentgenograms of the chest showed no abnormalities. A cover slip preparation of the fresh purulent material showed no mycelia, spherules or yeast cells. Curetting of the sinuses showed no sulfur granules or mycelia. Culture on Sabouraud's medium showed no fungi, but heavy growths of Staphylococcus aureus and hemolytic streptococci were observed. Inoculation of guinea-pigs gave negative results for tuberculosis and fungous diseases. The Wassermann reaction of the blood was negative. A biopsy showed pyoderma.

The diagnosis is pyoderma of pseudoblastomycetic type.

There was little response to the usual treatment for pyoderma. For the past six weeks the patient has received a saturated solution of zinc peroxide in a 5 per cent solution of pyrophosphate; this treatment has caused about 60 per cent involution of the lesions.

DISCUSSION

DR. H. V. ALLINGTON: I feel that the condition is probably a specific granulomatous process; absolute diagnosis depends on the results of the laboratory examinations

DR. MERLIN MAYNARD, San José, Calif.: Was the diagnosis of acne conglobata considered?

DR. G. V. KULCHAR: That diagnosis might be considered, I suppose. On the other hand, there are not the discrete cystic lesions seen in acne conglobata. This patient was presented not for diagnosis but to show the effect of the treatment introduced by Melenez, namely, use of a saturated solution of zinc peroxide in a 5 per cent solution of pyrophosphate. The response from the treatment has been remarkable. There has been a symptomatic response as well as regression in the lesions.

**Verrucous Type of Lupus Vulgaris.** Presented by DR. F. H. STIBBENS, Oakland, Calif.

Maria A., aged 55, an obese Mexican widow, came to the dermatologic clinic at the Oakland Health Center on Feb. 10, 1936, complaining of a large badly infected lesion on her right arm.

The disease is said to have developed over a period of four or more years, starting over the tip of the elbow, and gradually extending until practically the whole arm was involved for 5 inches (12.5 cm.) on each side of the joint. No description of the appearance of the original lesion was obtainable.

When the patient was first seen at the clinic, the entire lesion was covered with thick rupia-like crusts and bathed in pus. Over the olecranon was an area about 2 inches (5 cm.) in diameter and ½ inch (1.3 cm.) high, showing as a

verrucous mass. The edges of the entire lesion were circinate and raised above the surrounding tissues, and they showed apple jelly nodules in many areas. There was a decided tendency to healing in the central portion. Scrapings and culture were negative for fungi or other parasites.

The Wassermann reaction was negative on two occasions.

On March 6 the patient was transferred to the Highland Hospital, where a biopsy was made. The report, submitted by Dr. Gertrude Moore, was as follows: "The specimen submitted was a section of skin which microscopically showed areas of marked thickening of the surface and infiltration of the subcutaneous tissues with inflammatory cells of all types. There were places where plasma cells were numerous, but lymphocytes were the inflammatory cells most commonly observed. There were numerous giant cells of the Langhans type, a few of which showed rather marked cellular caseation. Epithelioid cells were present but not prominent, and no true tubercle formation was made out. While this lesion was not typical of tuberculosis, none of the higher organisms were observed, and none of the common granulomatous inflammations fitted better into the picture from a histologic standpoint. The diagnosis was chronic granulomatous infection."

The patient remained at the Highland Hospital until May 23 and then returned to the clinic, the lesion being about half healed. Since that date, healing has continued as a result of application of pure phenol and trichloro-acetic acid.

On June 30 the patient complained of pain in her back and gluteal region, and she was referred to the medical clinic for another physical examination. At this examination internal hemorrhoids and a systolic heart murmur were found, but no positive diagnosis was made.

On July 20 there were burning and frequent micturition, and the patient was referred to the urologic clinic, where a large cystocele and a "growth on the urethra" were found. Bleeding occurred on catheterization, but no description of the tumor was given.

The medical and urologic findings are believed to have no bearing on the dermatologic condition.

DISCUSSION

DR. F. H. STIBBENS, Oakland, Calif.: There is nothing definite in this case. The biopsy showed simply granulation tissue, with no picture typical of tuberculosis. Cultures and inoculations of guinea-pigs gave negative results. The interesting part is that healing has resulted simply from applications of phenol and trichloro-acetic acid. The rash on the elbow has decreased remarkably within the past month.

**A Case for Diagnosis.** Presented by DR. C. E. SCHOFF, Sacramento, Calif.

A resident of Sacramento, Calif., aged 80, a widow, is rather stout but says that she has lost 20 pounds (9 Kg.) in the last few months. She complains of small tumor masses in the skin of the neck, chest, shoulder region (as far down as the breast areas), axillary spaces, upper posterior thoracic region and upper portion of the abdomen. There are also a few scattered lesions on the thighs. The patient states that the lesions started about two years ago at the base of the neck. When she first noticed them there were four or five lesions present. Itching attracted her attention. She says that they form rapidly, that in due course of time the itching and the swelling subside and that the lesions then turn blue. From this history of onset there has been progressive development of these lesions over the parts mentioned.

The tumors vary in size from just palpable shot-like lesions to lesions the size of an almond. The skin over the larger lesions appears to be mildly erythematous, the erythema readily fading on pressure. The epidermis appears to be normal in its continuity. There is no atrophy or umbilication. The tumors, which are sharply defined and hard on palpation, seem to be an incorporate part of the corium. There are no subjective symptoms on palpation. There is no involvement of the mucous membrane.

The Wassermann and Kahn tests were negative. The urine was practically normal, although the specimen submitted showed a faint trace of albumin and dextrose. Examination of the blood gave the following results:

| | |
|---|---|
| Red blood cell count | 4,060,000 |
| Hemoglobin content (Newcomer) (69%) | 11.8 Gm. |
| Color index | 0.86 |
| Morphologic characteristics of red blood cells: | |
| Changes in size, none | |
| Changes in shape, none | |
| Hemoglobin content, good | |
| Basophilia, none | |
| Immature forms, none | |
| Parasites, none | |
| White blood cell count | 15,600 |
| Differential count: | |
| Neutrophils: | |
| 1. Segmented forms | 39.5% |
| 2. Staff forms | 1.5% |
| 3. Metamyelocytes | % |
| Total | 41.0% |
| Eosinophils | 0.5% |
| Basophils | 0 % |
| Monocytes | 2.0% |
| Lymphocytes | 56.5% |

Although the percentage of lymphocytes was increased, their forms showed no changes suggesting leukemia.

Sections from a recent lesion and from one of the first lesions manifested are shown.

DISCUSSION

DR. H. E. MILLER: I consider the condition to be probably lymphoblastoma, perhaps aleukemic leukemia.

DR. C. E. SCHOFF, Sacramento, Calif.: The possibility of a leukemic condition was considered. Examination of the blood showed about 16,000 leukocytes with a preponderance of lymphocytes and no changes in the structure of the cells. Material for biopsy was obtained from a recent and from an older lesion, and the histologic picture of the two specimens were practically the same. There was little connective tissue formation. There was a preponderance of collagen throughout the lesions. It has been impossible to identify any changes originating in the nerve sheath which would suggest true Recklinghausen's disease. The diagnosis is undetermined because it does not fit in particularly with any of the types of cutaneous lymphogranuloma. The staining particularly brought out the preponderance of collagen in the tissues. Pathologists were unable to define the picture as representing any pathologic entity.

**Lingua Geographica.** Presented by DR. F. H. STIBBENS, Oakland, Calif.

Joe C., aged 5 years, was admitted to the pediatric clinic on Dec. 10, 1935, where a diagnosis of thrush was made and he was treated for about three months without improvement. Cultures and smears for Monilia gave negative results.

He was then transferred to the dermatologic clinic where he was found to be suffering from a typical geographic tongue. The patient is presented for suggestions as to treatment.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: Dr. Howard Fox originally suggested roentgen treatment for this condition.

DR. G. V. KULCHAR: That therapy is of considerable value.

DR. H. E. MILLER: I should leave the lesion alone. I should hesitate to treat a 5 year old child with roentgen rays.

DR. MERLIN MAYNARD, San José, Calif.: I have seen lesions such as these treated with solution of benzoic acid. I do not think there is much one can do except to build up the patient.

**Lupus Erythematosus.** Presented by DR. F. H. STIBBENS, Oakland, Calif.

Mrs. Mary J., aged 69, was admitted to the dermatologic clinic of the Oakland Health Center on Nov. 21, 1932. She complained of indigestion, abdominal pain and cramps and multiple cutaneous lesions of the face. Examiners in the medical clinic made a tentative diagnosis of chronic cholecystitis and then referred the patient to the dermatologic clinic, where the lesions were diagnosed as lupus erythematosus.

The history of onset of the disease is interesting. About twenty or twenty-five years ago the patient lived in the mountainous part of northern California. While she was skating one winter her face and hands had become frost bitten. She dashed into her home and held her mittened hands to a fire and then clapped them to her face and burned the skin. Later, reddened areas developed wherever her gloves had touched the skin. These areas alternately cleared and reddened each year for several years, the pigmentation gradually lasting longer, until the lesions became chronic.

Typical lupus erythematosus is present over the nose, the left cheek, the left eyebrow and the regions anterior and posterior to each ear.

In August and September 1933 the patient was given eight intravenous injections of gold and sodium thiosulfate. Symptoms of poisoning occurred, and the treatment had to be discontinued.

In February 1934 intramuscular injections of bismuth subsalicylate were started, and improvement began immediately. She has received ninety injections.

She is presented to show the result.

DISCUSSION

DR. H. C. COE, Oakland, Calif.: I think that a gratifying result has been obtained by this treatment. She has received much bismuth, but the result has been satisfactory.

**A Case for Diagnosis (Dermatitis Medicamentosa?).** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

Mrs. M., aged 43, has over the right breast circinate lesions with an erythematous border which suggest dermatitis medicamentosa due to phenolphthalein. The patient has recently taken this drug, but she doubts that she had taken it before the many attacks which she has had since the age of 9 years.

In 1930 she had a serious attack of an acute dermatitis, probably lupus erythematosus disseminatus, for which she was referred to me by Dr. Alderson. She was ill for six months but finally recovered.

DISCUSSION

DR. H. E. MILLER: I should provisionally call the condition a toxic dermatitis.

DR. H. J. TEMPLETON, Oakland, Calif.: I consider it to be dermatitis medicamentosa, probably due to phenolphthalein. There is a definite history of ingestion of phenolphthalein, but the fly in the ointment is that the patient has had attacks of this eruption since she was 9 years old and that phenolphthalein was not so widely used at that time.

It is of interest that she was ill for six months with an acute disseminated lupus erythematosus and was one of the few patients I have known to recover. Recovery occurred after abscessed teeth were removed.

DR. HARRY E. ALDERSON: This attack may be a forerunner of a frank erythema multiforme. The lesions are slightly suggestive. When she had lupus erythematosus several years ago, early in the process there were lesions somewhat similar to those seen tonight. Possibly she is now getting ready for another attack.

**A Case for Diagnosis.** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

Mrs. E. I. was seen on Sept. 8, 1936, because of areas of exfoliation of the palms from the size of a pinhead to that of a finger-nail. These had been present for two months. She had also had some exfoliation between her toes which her physician had diagnosed and treated as dermatophytosis.

Numerous dry scaling areas measuring from 1 mm. to 1 cm. in diameter give one the impression that she has a squamous dermatophytosis (exfoliatio areata manus), but closer study reveals that the earlier lesions are hard cornlike bodies which are not quite in keeping with that diagnosis. Scrapings from the lesions showed only mosaic fungi. The Kline test was negative.

The diagnoses of dermatophytid and lichen corné have been considered.

DISCUSSION

DR. MERLIN MAYNARD, San José, Calif.: My feeling is that the condition is primarily embolic. I do not think that deep cornous lesions of that type would develop without the presence of something similar to erythema multiforme. Papulonecrotic lesions may, of course, look like that. The lesions are too deep to be compatible with a diagnosis of dermatophytosis.

DR. HARRY E. ALDERSON: Is there any evidence of systemic gonorrhea?

DR. H. J. TEMPLETON, Oakland, Calif.: I am sorry that I have not considered that possibility. I appreciate the suggestion.

DR. THOMAS J. CLARK, Oakland, Calif.: This condition would ordinarily be classified as chronic eczema. There are definite scattered, independent lesions. The patient complains of a certain amount of nervous reaction. She says that there is a tingling sensation rather than itching.

DR. FRANCIS TORREY: I think that one should consider a toxic or an embolic cause. Whether the condition is due to some specific focus of infection or is toxic should be considered.

DR. H. J. TEMPLETON, Oakland, Calif.: I thank the members for their suggestions. I shall have an internist examine the patient thoroughly.

**Xanthoma Tuberosum Multiplex in an Infant.** Presented by DR. H. V. ALLINGTON.

Dorothy Ann, aged 2 years, has an uneventful history except for her cutaneous lesions. She presents numerous well circumscribed smooth lemon-yellow papular lesions over her body, especially on the upper portion of her trunk. These vary in size up to approximately 1 cm. in diameter, the largest being elevated to the extent of from 5 to 6 mm. They first appeared when the patient was about 6 months old and have increased in size and number. They cause no symptoms. Repeated examinations of the urine have given negative results. The sugar content of the blood was 76 mg. and the cholesterol content 219 mg., per hundred cubic centimeters of blood. The blood count showed 81 per cent hemoglobin, 6,200 white cells and 4,470,000 red cells. The differential count showed 46 per cent polymorphonuclears, 5 per cent eosinophils and 49 per cent small lymphocytes.

Sections are presented.

DISCUSSION

DR. H. V. ALLINGTON: This case is interesting, for one seldom sees so many lesions in so young a child. I should appreciate suggestions as to treatment.

DR. HARRY E. ALDERSON: Would Dr. Allington care to try insulin?

DR. H. V. ALLINGTON: I think that I should leave that up to the pediatricians' judgment. If they are willing, it might be tried, although the sugar content of the blood during fasting is a low normal. The patient was on a low cholesterol diet, however, for quite a while, and no apparent change in her condition resulted.

**Lichen Planus Confined to the Mouth.** Presented by DR. STANLEY R. TRUMAN, Oakland, Calif. (by invitation).

Miss D., a student at the University of California, a registered nurse, has noted whitened areas of the buccal mucosa on both sides for four months. She smokes moderately. Both gold and silver fillings are present.

On the buccal mucosa on the right side the lesions have the lacelike appearance which suggests lichen planus. No lesions are present on the skin. Besides lichen planus the possibility of leukoplakia and of lesions due to electrolysis from gold and silver was considered.

No biopsy or complement fixation test has been made, as the patient was first seen yesterday.

DISCUSSION

DR. L. R. TAUSSIG: I agree with the diagnosis. The treatment of lichen planus of the mucous membrane is unsatisfactory. The lesions do not respond to the usual methods.

**Pyoderma.** Presented by Dr. H. V. Allington.

Alice B., aged 7 years, has no significant history or abnormalities aside from those relating to her skin. She has superficially ulcerated, irregularly annular lesions over the knees and on the lower lip and chin, and one or two lesions are scattered elsewhere on her extremities. They are dull red, have elevated margins and ooze considerably, tending to form dry honeycomb crusts. They have been present for about two months. They appear as small erythematous papules which quickly soften and ulcerate in the center and then increase in size by peripheral extension. So far microscopic and cultural examination has revealed only Staphylococcus albus. A culture for the Klebs-Löffler bacillus has been made, but the report is not available yet.

As a result of treatment a few of the lesions have healed, leaving superficial scars. Most of them have thus far resisted treatment, which has included trial of most of the remedies used for pyoderma. We have increased the vitamin content of the patient's diet and prescribed solution of potassium arsenite U. S. P. and generalized ultraviolet irradiation. Three fourths of a skin unit of roentgen radiation has been given to the lesions. The patient has received one injection of foreign protein.

She is presented for suggestions for further treatment.

DISCUSSION

Dr. Merlin Maynard, San José, Calif.: The patient's mother told me that she had given the child persang. Quite likely that drug contains iodine. I feel that the condition is pyoderma, though the possibility of an iododerma must not be forgotten.

Dr. H. V. Allington: I questioned the mother about the use of persang and found that the patient took it only after the lesion had appeared. She did not know whether iodized salt was used in the home, but she promised to make sure that it would not be.

Dr. Thomas J. Clark, Oakland, Calif.: I think the disease is chronic impetigo contagiosa. As to therapy, I should use compresses of boric acid and then apply a powder composed of 1 drachm (4 Gm.) of powdered alum in 1 ounce (28 Gm.) of zinc stearate.

Note.—Dr. Thomas Clark's suggestions were carried out for ten days, and little change resulted. Then the patient was confined to bed, and continuous dressings wet with a 3 per cent aqueous solution of urea were applied to the lesions. She recovered promptly, the lesions disappearing eight or nine days after the treatment was begun.

**Multiple Sarcoid of Boeck.** Presented by Dr. F. G. Novy Jr., Oakland, Calif., and Dr. H. J. Templeton, Oakland, Calif.

Miss M., aged 20, a student at the University of California, has received weekly injections of gold sodium thiosulfate for six months because of sarcoids. She was presented before this society previously. At that time cutaneous, nasal and palatal lesions were present. A thorough study revealed no evidence of tuberculosis. In previous therapy use had been made of arsenic and tuberculin. One area on the right arm was treated experimentally with unfiltered roentgen radiation, but the lesions failed to respond.

Therapy with a gold compound has caused the lesions to retrogress slightly, but improvement has been slow.

Suggestions as to therapy are requested.

DISCUSSION

Dr. H. J. Templeton, Oakland, Calif.: The members may recall that this patient has received neoarsphenamine, bismarsen, a gold preparation, tuberculin, ultraviolet radiation and cod liver oil. Recently she has had several attacks of

fever (not induced). She thought her lesions retrogressed a little after the fever. Therefore, I wonder whether I should be justified in trying fever therapy for sarcoid.

DR. G. V. KULCHAR: I think there is a good rationale for fever therapy for sarcoid. Good results from fever therapy are not dependent on the fever itself but on the effect of the fever on the reticulo-endothelial system. It is interesting to know that ethyl esters of Hydnocarpus, which are used in leprosy, and chaulmoogra oil are being used for sarcoid.

**A Case for Diagnosis (Lichen Planus?).** Presented by DR. HARRY C. COE, Oakland, Calif.

Mrs. S., aged 76, a German widow, complains of generalized itching cutaneous lesions which have been present for six years.

She has had scarlet fever and has suffered from frequent attacks of tonsillitis. A complete hysterectomy necessitated by a tumor was performed when the patient was 35. She has suffered from chronic constipation for years. Otherwise her past history is unimportant.

About six years ago she had sciatica. Later a papular eruption developed on her legs and spread until it became generalized. She has spells of intolerable itching which cause her to scratch with a brush until she is relieved. She has consulted many dermatologists and has received all kinds of treatment.

The feet, legs, thighs and lower half of the trunk are covered with papular lesions. Similar lesions are scattered over the chest and arms. The early primary lesion is a flat, angular purplish papule. The older lesions are larger, round and lighter. The lesions become confluent, and the skin is thickened and dry. There is a tendency to hyperkeratosis.

Physical examination gave negative results.

The blood count and the hemoglobin content were within normal limits. The urine was normal and the Wassermann reaction negative. The basal metabolic rate was + 3 per cent.

DISCUSSION

DR. H. J. TEMPLETON, Oakland, Calif.: I saw this patient five or six years ago. I considered the following diagnostic possibilities: (1) prurigo, (2) dermatitis herpetiformis and (3) lichen planus. I now lean to the diagnosis of prurigo, not prurigo nodularis but a prurigo with a toxic background.

DR. H. C. COE, Oakland, Calif.: This patient has been seen by several dermatologists. No one has been able to make a diagnosis. She suffers discomfort from the itching. I did have some success with an equilibrated salt diet. I put her on that for a while, and the eruption cleared up with the exception of a few scattered lesions. She stopped her diet, and since then the condition has recurred.

DR. H. J. TEMPLETON, Oakland, Calif.: Whether the condition is prurigo or dermatitis herpetiformis, there is some cause for it and attempts at ascertaining the cause should be continued.

When my co-workers and I took care of this patient we examined her as thoroughly as we could; we also had an internist and an allergist examine her. She followed elimination diets, received autohemotherapy and took Barbour's urinary proteose, all with no benefit.

Some toxic process is responsible, and I think special efforts should be made to find the cause.

**Gumma of the Knee.** Presented by DR. HARRY C. COE, Oakland, Calif.

**Tuberculosis Cutis (Lupus Vulgaris or Sarcoid).** Presented by DR. H. J. TEMPLETON, Oakland, Calif.

## BRONX DERMATOLOGICAL SOCIETY

PAUL GROSS, M.D., *President*

*Feb. 25, 1937*

HENRY SILVER, M.D., *Secretary*

**Morphea.** Presented by DR. ADOLPH ROSTENBERG.

M. E., a woman aged 31, states that the present cutaneous condition began four years ago, soon after the birth of her first child, which was difficult and protracted. The menstrual periods have since been irregular. The patient complains of pain in the lower portion of the abdomen, in the region of the ovaries.

On the upper part of the thighs are about a dozen irregular oval lesions, some isolated and some fused, forming irregular plaques. The skin is white or ivory colored, markedly wrinkled and atrophic but hard, parchment-like to the touch. Each lesion is surrounded by a violaceous border. Examination of the blood and urine gave negative results. The Wassermann reaction of the blood was negative.

DISCUSSION

DR. WILBERT SACHS: I cannot make a definite diagnosis. If the atrophic type of scleroderma can develop in a relatively short time I suggest that diagnosis. I do not believe that the condition is either morphea or one of the group of chronic atrophic dermatitides of which Csillag's disease is but one example.

DR. THEODORE ROSENTHAL: The lesions are dull white, scaly and slightly infiltrated. Patients with morphea usually present smooth lesions with a glistening appearance. I am more inclined to make the diagnosis of lichen sclerosus than that of morphea.

DR. ARTHUR SAYER: The lesions on the sides of the thighs show a definite violaceous border which is characteristic of morphea. Other lesions on the thighs show a uniform glistening white appearance, have a cardboard-like feel and closely resemble the cardboard-like scleroderma of Unna. This patient thus has two characteristic types of scleroderma.

DR. SAMUEL FELDMAN: I fail to see any resemblance to lichen sclerosus. To justify a diagnosis of lichen sclerosus, there must be a horny plug or a dilated follicle where such a plug has fallen out. Besides, patches of lichen sclerosus are made up of a coalescence of a number of papules of lichen planus, and if one looks carefully at a patch of lichen sclerosus one invariably sees the line of division between individual papules. This patient's lesions have definite sharp borders without any outlying papules and without any line of division within the patch. Neither is there any evidence of a dilated follicle or of a horny plug. I am inclined to agree with Dr. Sachs that if there is such a condition as an atrophic type of scleroderma, in which atrophy develops rapidly, this patient's disease is of that type. The smaller lesions are more typical of scleroderma.

DR. DAVID L. SATENSTEIN: On the patient's left thigh there is a fairly firm whitish glistening lesion, irregular but sharply marginated, about 4 inches (10 cm.) in diameter. Surrounding this area on the same thigh and on the opposite side, there are irregular lesions of various sizes with a fine erythematous margin. On the lower surface of the right breast there are lesions which appear to be atrophic and do not show infiltration or scaling. There are also small lesions made up of fine slightly scaly papules. The history that I obtained was that the white sclerotic lesions had been present for a long time, the lesions on the thighs for only three or four months and those on the breast for only a few weeks. I do not know of any kind of scleroderma or morphea that goes on to atrophy in so short a period. I do not see anything in these lesions that suggests scleroderma, and I am sure that the histologic examination will bear this out. I am of the opinion that this process is one of atrophy and belongs to the group of dermatitis chronica atrophicans.

DR. DAVID BLOOM: The eruption differs from that seen in a patient whom I presented two months ago before the section of dermatology and syphilis of the New York Academy of Medicine with the diagnosis of lichen sclerosus et atrophicus. In my patient there were discrete angular and umbilicated papules, violaceous or ivory white, in addition to the roundish or oval plaques formed by coalescence of these lesions. The centers of the plaques showed follicular plugs. The eruption in Dr. Rostenberg's patient has many features of morphea, and in addition there is atrophy in some of the lesions. I therefore agree with the diagnosis as presented.

DR. HENRY SILVER: The fact that somewhat atypical manifestations of a familiar clinical entity like morphea elicit such differences of opinion is sufficient proof that the subject of localized scleroderma needs clarifying. Moreover, similar varied opinions are met with throughout the literature. The many described entities, such as lichen sclerosus of Hallopeau, dermatitis lichenoides chronica atrophicans of Csillag, lichen albus of von Zumbusch, lichenoid scleroderma, described by Wise, cardboard-like scleroderma of Unna and white spot disease, are more confusing than clarifying. In the absence of a known etiologic factor, differentiation must be maintained on purely clinical and histologic grounds. In analogy to the circumscribed atrophies, circumscribed scleroderma can be divided into a plaque variety and a small papular or lichenoid variety. In the macular atrophies Dr. Chargin and I succeeded in establishing two definite clinical entities, and the small type scleroderma can be similarly classified. In the case under consideration the condition is fairly characteristic of morphea in spite of the presence of slight scaling.

DR. ARTHUR SAYER: I believe that a biopsy should give definite information regarding the diagnosis in this case. When Dr. Wise studied this group of conditions four or five years ago, he discussed all the types mentioned tonight. He stated that histologic examination was important and that it helped to differentiate the conditions from each other. The identity of lichen planus of the various types is easily proved on account of its definite histopathologic picture. With scleroderma, the characteristic degeneration of the collagen fibers enables one to establish the diagnosis. Some of the other diagnoses suggested can be eliminated by exclusion.

DR. DAVID L. SATENSTEIN: In scleroderma the elastic tissue remains intact. The development of the atrophy consumes a considerable period. The microscopic picture is fairly definite in those conditions. I had the opportunity of making the histologic examinations for Dr. Wise; I saw most of the conditions which Dr. Silver enumerated and studied them histologically. I am therefore convinced that there is an essential difference between the atrophies and the sclerodermas.

DR. ADOLH ROSTENBERG: I thought the condition was clearcut and expected that every one would agree with the diagnosis. To me it looks like classic morphea.

**Lupus Erythematosus in a Child.** Presented by DR. HENRY SILVER.

E. P., a girl aged 11 years, presents an eruption on the face, which becomes aggravated during the summer. The eruption consists of ill defined, irregular patches; these are as a rule erythematous but at times become covered with an adherent scale, and it is then that they are fairly typical of lupus erythematosus. On Feb. 6, 1937, new lesions appeared on the palms in the form of a reticulated pattern of red dots and points.

The past history revealed that the patient had scarlet fever, chickenpox, measles, whooping cough, frequent colds and otitis media. A tonsillectomy was performed when she was 2 years old.

Physical examination gave negative results. Examination of the blood showed 83 per cent hemoglobin, 4,390,000 red cells and 8,400 white cells. The differential

count showed 65 per cent polymorphonuclears, 28 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. Examination of the urine gave negative results.

Roentgenograms of the skull showed the sella turcica to be normal in size, shape and position. There were no abnormalities in the clinoid processes. There were no unusual shadows in the cranial vault or in the bones of the calvarium. Roentgenograms of the chest showed no abnormalities. Tests with venom to determine the capillary fragility of the lesions gave negative reactions.

The patient has been given a salt-poor diet, with a special salt mixture and tablets of an iso-ionic mixture of calcium, potassium and magnesium salts. She has received till now twelve injections of bismuth subsalicylate.

DISCUSSION

DR. HENRY SILVER: The reason for presenting this patient is to show the differences that evidently exist, but are rarely mentioned, in regard to the clinical picture, the course and the therapeutic response of the chronic type of lupus erythematosus in children.

DR. MAURICE UMANSKY: Cummer reviewed the statistics on lupus erythematosus in children and stated that between 3 and 12 per cent of all cases of lupus erythematosus occur in children. All three types, the chronic discoid, the subacute and the acute, affect children. There is always grave danger that this disease will become disseminated. I had under my care a child aged 7 years with an eruption resembling erythema multiforme on the face which followed a sunburn; it became generalized, and five months later the child died at the Mount Sinai Hospital of disseminated lupus erythematosus. The mother of this child suffered years ago from a discoid form of lupus erythematosus which yielded to treatment.

DR. VAN ALSTYNE H. CORNELL: I believe that often, in the case of young persons especially, a diagnosis of lupus erythematosus is made when in reality the condition is seborrheic eczema with a distribution resembling that of lupus erythematosus. The reverse may happen also. The correct diagnosis is most important when the disease occurs in young persons, so that the proper management may be instituted early.

DR. ARTHUR SAYER: I believe the point that Dr. Cornell brought up is rather important and should be emphasized. Those who have seen lupus erythematosus in children are forcibly impressed by the fact that the lesions are different from those in adults. There is no atrophy of the skin, at least in the early stage of the disease, and the classic picture of adherent scales and telangiectases, as seen in adults, is lacking. Dr. Umansky mentioned that lupus erythematosus in children is a rather serious condition because in so many of them the disease eventually has a fatal termination. I agree with that statement.

DR. LOUIS CHARGIN: Lupus erythematosus in children differs from that observed in adults. In adults either the acute or the discoid variety is present. In children the disease appears in a subacute form and only after a varied course and a prolonged period may assume the discoid aspect.

DR. DAVID BLOOM: The child whom I presented at the last meeting of the society had a more superficial form of lupus erythematosus than the patient of Dr. Silver. Treatment with gold preparations may lead to dissemination and ultimately to death, as I had recently the misfortune to observe.

DR. FRANK CROSS: I fully agree with most of the speakers that lupus erythematosus in children is much more serious than it is in adults. While I agree with the remarks of Dr. Bloom, I wish to mention an experience in which therapy with a gold compound produced a severe scarlatiniform reaction accompanied with a temperature of 106 F. The patient recovered, however, and the eruption cleared up. The cure was evidently a good effect of the fever.

DR. PAUL GROSS: What is the essential theoretical and practical meaning of the difference between lupus erythematosus in children and that in adults? Is it

the difference in the immune reaction or that in the physiologic function of the skin which accounts for the facts mentioned here? The name seborrhea congestiva should be avoided, since it is misleading and antiquated.

DR. HENRY SILVER: The interesting discussion clearly shows that there is general agreement with regard to the clinical features of lupus erythematosus in children. Dr. Umansky mentioned that the occurrence in children ranges from 3 to 12 per cent. This wide range can be explained on the basis of the general occurrence of lupus erythematosus. It is known that in certain countries the disease is more frequent than in others and that, paradoxically, in tropical countries lupus erythematosus is practically unknown. Incidentally, it is interesting to note that more cases are observed in girls than in boys and that the ratio of 3 to 1 statistically established for adults is maintained for children. The characteristic clinical picture of the disease, namely, sharply defined patches, hyperkeratosis, telangiectasia and atrophy, is seldom well pronounced in children. For a long time there is only erythema and hardly any scaling. The eruption at this stage often presents a difficult diagnostic problem, and such a diagnosis as erythema multiforme, erythema toxicum or erythema solare are not infrequently made. I agree with Dr. Gross that seborrhea congestiva is a misleading name. To this day the French accept Biett's name *érythème centrifuge* for the superficial type of lupus erythematosus.

The therapeutic problem is even more important, because with it is associated the prognosis. It can be definitely stated that lupus erythematosus in children does not readily respond to usual accepted forms of therapy. Gold preparations are not well tolerated and are of little benefit. Bismuth compounds, on the other hand, are well tolerated but give indifferent results. I have tried to combine bismuth treatment with a salt-free diet and have been slightly more successful, but treatment must be carried out for six months or more. The salt-free diet is combined with administration of tablets containing calcium, potassium and magnesium salts and the use of a special salt mixture. Solid carbon dioxide should not be used since local destructive methods should not be employed for an erythema-like eruption. It is important to stress that most children with lupus erythematosus are sensitive to natural and artificial sunlight. In view of this sensitivity to light, it is desirable to protect the face and exposed parts of the body with an ointment.

**Varioliform Syphilid.** Presented by DR. MAX B. KAMPF.

W. M., a man aged 20, was sexually exposed to syphilis about two months ago. Ten days later he noticed a urethral discharge and immediately went to his physician for treatment. He received about ten intravenous injections, two injections being given each week. At the end of the eighth treatment there developed lesions on both elbows (apparently at the site of the injections), which were rapidly followed by lesions on the genitals, trunk, face, extremities and soles. Within one week the eruption became generalized.

The lesions are dirty brownish red rather flat-topped papules, the size of a pea or larger. There are many varioliform lesions which lack umbilication. The pharynx shows dirty grayish mucous patches.

Reports on the Wassermann and dark field examinations have not yet been received. I am trying to ascertain what type of medication the patient received before he presented himself at the Fordham Hospital for treatment.

NOTE.—The laboratory report showed that the Wassermann reaction of the blood and that of the spinal fluid were 4 plus. The dark field examination for spirochetes gave negative results. The smear of material taken from the urethra showed gonococci.

DISCUSSION

DR. LOUIS CHARGIN: Aside from the absence of general symptoms the eruption differs from that of smallpox. The lesions are not of the same age or of the same size, and one misses the umbilication present in the lesions of smallpox. The fact

that the backs of the hands and the forehead are comparatively free also points against the diagnosis of smallpox. I do not think that the patient's statement with regard to the duration of the infection is correct. The infection is three or four months old.

DR. ARTHUR SAYER: It is interesting to note that this man has a large tattoo mark on the left arm in which there are four papular syphilitic lesions. Each of these papules is located on the blue part of the tattoo mark, and none is seen in the red areas. The red tattoo is done with red mercuric sulfide, which prevents the local development of syphilitic lesions.

DR. ADOLPH ROSTENBERG: It seems to me that the diagnosis of smallpox should not be seriously considered, since the patient would necessarily be bedridden at this time. Moreover, the lesions would be uniformly pustular and not papular. Without doubt, the eruption is one of syphilis modified by the injections he has received, although it is not definitely established that the drug used was arsphenamine. I do not think that this is an arsphenamine-resistant syphilid.

DR. DAVID BLOOM: To corroborate Dr. Chargin's remarks I wish to state that I remember at least two patients with extensive pustular syphilis of this type who were referred to the Bellevue Hospital by physicians of the Willard Parker Hospital, where they had been sent with the diagnosis of variola. Not only the picture of the eruption in the beginning but the high temperature which is usually associated with this type of eruption is misleading.

DR. LOUIS CHARGIN: On a number of occasions I have had to differentiate this type of eruption from smallpox at the Kingston Avenue Hospital, to which patients suspected of having smallpox are sent; at the outset this may be extremely difficult, since the type of eruption and the associated general symptoms, including high temperature, may be alike in the two diseases. I agree that in this case the diagnosis of syphilis is fairly clearcut.

DR. PAUL GROSS: Dr. Chargin's statements are important. An eruption of syphilis and one of smallpox resemble each other also in regard to location, as local irritation plays an important part in both. The appearance of such an eruption after satisfactory antisyphilitic treatment is unusual but not quite as rare as one is led to believe. A change to a different type of therapy may rapidly influence the eruption.

DR. MAURICE UMANSKY: I understand that the patient received antisyphilitic treatment from a physician in the form of intravenous injections. They evidently were not sufficient in number or strength to suppress the appearance of a papulopustular exanthem, which the patient shows tonight. They may even have contributed to the unusual intensity of the eruption. There is no reason to believe that this is a case of treatment-resistant syphilis, unless further treatment does not produce the effect which one expects to see in a case of secondary syphilis.

DR. VAN ALSTYNE H. CORNELL: The assumption that this may be a case of arsphenamine-resistant syphilis lacks proof. The patient has received ten injections, but it is not known whether the drug injected contained arsenic or not.

DR. MAX B. KAMPF: I have written to the physician who treated this patient with intravenous injections but have thus far not received a reply. I do know that he has apparently not received injections of a bismuth preparation, as he definitely states that he received no intramuscular injections of any kind.

**Dermatitis Herpetiformis (?).** Presented by DR. ADOLPH ROSTENBERG.

S. M., a man aged 33, under the care of Dr. Adolph Rostenberg, Jr., presents a generalized eruption, which for the past three years has appeared each December and lasted until the advent of warm sunny weather. During the attacks the areas involved show occasional improvement, but they never clear entirely.

The present attack began about Dec. 1, 1936. The eruption appeared first on the anterior aspects of the legs and then spread to the thighs, arms, abdomen, ears

and hands in the order given. The eruption is generalized and markedly symmetrical and shows a distinct tendency to grouping and to herpetiform arrangement. It consists of erythematous plaques covered with pustules, vesicles and crusts. In places there are individual, discrete papular or pustular lesions which arise from what appears to be healthy skin. There is no pigmentation. At times there is intense itching. During the last week the clinical appearance of the eruption changed from a vesicular to a more variegated appearance, dry papular plaques predominating. There is no history of ingestion of drugs. Examination of the blood and urine gave negative results.

DISCUSSION

DR. LOUIS CHARGIN: I am much interested in this case. Almost every winter for many years I have observed patients with this type of eruption. As a rule the eruption is papulovesicular and appears in small and large patches, involving chiefly the extremities and occasionally the face. The eruption is associated with considerable itching; it lasts for a long period during the winter and often disappears with the onset of warmer weather. These eruptions are not influenced by therapy. I do not regard them as a type of dermatitis herpetiformis, to which they have but a remote resemblance. The seasonal appearance, the eczematoid character and distribution of the eruption, the spontaneous disappearance in the summer and the lack of response to therapy are not like the characteristics of dermatitis herpetiformis. I have known this condition to be diagnosed as dermatophytosis or ids, and I do not agree with that practice.

DR. SAMUEL FELDMAN: I fully agree with the view expressed by Dr. Chargin. This condition is frequently observed but as a rule is not diagnosed as Duhring's disease. In a patient with dermatitis herpetiformis of three years' duration one would expect pigmentation, even if no scars were present. Neither of these features is present in this patient.

DR. CHARLES WOLF: In my opinion this condition does not warrant as pessimistic an outlook as one would be led to believe from the remarks made so far. I think the difficulty is one of diagnosis. A thorough investigation of environmental factors would no doubt clear up the diagnosis, particularly in view of the fact that the condition spontaneously improves in the summer. I believe that this patient suffers from a contact dermatitis. The eruption has none of the earmarks of dermatitis herpetiformis.

DR. VAN ALSTYNE H. CORNELL: If Dr. Wolf assumes that this is a contact dermatitis, can he explain why the offending agent does not operate during the summer and is active only in the winter?

DR. CHARLES WOLF: In answer to Dr. Cornell, I am fairly certain that the etiologic agent is wool and that the patient has a dermatitis due to wool. In the winter persons cover themselves with wool blankets, and if the patient can discontinue that practice he will get well with bland ointments. I suggest that he should sleep between cotton sheets and under a quilt.

DR. HENRY SILVER: The etiology and treatment of eruptions that recur during the winter is unfortunately not as simple as Dr. Wolf would have one believe. To assume that this patient suffers from a contact dermatitis which is caused by wool blankets is, I admit, convenient. Careful study of the patient's home environment, including thorough patch tests, failed to give the necessary proof. This was well demonstrated by Dr. Sulzberger and his co-workers for a similar group of cases which were thoroughly discussed at the last meeting of this society (ARCH. DERMAT. & SYPH. **36**:452 [Aug.] 1937). It is evident that these eruptions present a complex problem, and it is disheartening to admit that no one knows what they are, how to name them and what to do for them.

DR. ADOLPH ROSTENBERG JR.: I labeled the condition dermatitis herpetiformis because I did not know what else to call it. During the past week there has been quite a change in the clinical picture. When I first saw the patient there was a considerable amount of oozing; this has cleared up. The factors that favor the

diagnosis of dermatitis herpetiformis are the marked symmetry of the eruption, the marked grouping and the herpetiform distribution. If the condition is not dermatitis herpetiformis it is possibly a so-called inexplicable eczema. I have observed most of the cases which Dr. Sulzberger and Dr. Garbe have studied, and the condition in this case is qualitatively different from that in theirs. As to the possibility of contact dermatitis, I certainly should emphatically state that that diagnosis is not correct. First, I do not think the eruption has the general appearance of a contact dermatitis; second, the largest and most significant point is that individual lesions arise from absolutely normal skin. I have never seen a contact dermatitis—supposing Dr. Wolf means the same as I do by the term contact dermatitis—which had not some erythematous halos about the vesicles and the individual lesions. I agree with the majority of speakers that it is useless to make tests or carry out any sort of work-up from the testing point of view. At the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital tests are no longer made in these cases because the results are invariably negative.

**Extensive Naevus Flammeus.** Presented by Dr. Frank E. Cross.

D. P., a schoolgirl aged 14, an American of Italian descent, presents an extensive unilateral irregular port wine nevus which involves the entire right hand, the forearm and two thirds of the upper portion of the arm. The condition has been present since birth.

The patient is presented for suggestions as to therapy.

DISCUSSION

Dr. Frank E. Cross: Because of the extent and the location of the nevus, the condition presents a social as well as an economic problem, and suggestions with regard to therapy are requested. Treatment with infra-roentgen rays have been suggested. I feel that ultimately it will be necessary to resort to some means of artificially covering the lesion.

Dr. David L. Satenstein: If infra-roentgen rays are used all one can expect is a radiodermatitis. Because of its size, the lesion cannot be treated by electrocoagulation. Treatment with the water-cooled quartz mercury vapor arc lamp produces deep infiltration, and the results are not satisfactory. A method which my co-workers and I have been using and which offers some chance of success is to rupture the blood sinuses mechanically by means of the suction cup. The apparatus is inexpensive, and the technic is simple. After the skin is greased the cup is applied and suction produced until the area becomes black and blue. On successive periods this is repeated, and if the treatment is continued good results may be obtained.

Dr. Wilbert Sachs: I have treated quite a number of such lesions with the suction cup method. The results are encouraging. It is frequently difficult to induce patients to continue treatment because of the long time necessary to obtain good results.

**Lichen Planus-Like Postarsphenamine Eruption Subsequent to a Paravenous Infiltration.** Presented by Dr. Samuel Feldman.

W. S., a laborer aged 63, states that he has syphilis of long standing. The Wassermann reaction of the blood was 4 plus. On February 5 one of the hospital interns administered to the patient 0.2 Gm. of arsphenamine intravenously. The tissues at the point of injection became swollen and infiltrated. There was no breaking down of tissues, and the inflammation subsequently subsided.

On February 12 the patient received an injection in the other arm. Two days later there developed a papulovesicular eruption in the region of the elbow on the anterior surfaces of both arms and forearms, accompanied by marked exudation; it soon spread to the trunk and lower extremities. After the acute character of the eruption subsided lesions assumed the form of flat annular shiny and

violaceous papules with depressed centers. The condition is now typical of lichen planus. Only the knowledge that the patient has received arsphenamine medication and the vesicular appearance of the lesions at the onset make the diagnosis of true lichen planus doubtful.

DISCUSSION

DR. ADOLPH ROSTENBERG JR.: The question of sensitization to a drug, particularly to arsphenamine, after a paravenous infiltration, raises many theoretical considerations. In all cases of experimental sensitizations to a simple chemical, such as a drug, one has to deposit the allergen intracutaneously or subcutaneously (this includes mere painting of the surface of the skin). Direct deposition of the drug into the blood stream does not produce such sensitization. All physicians have seen many patients with paravenous deposits of arsphenamine, yet few with an arsphenamine dermatitis. As Dr. Feldman has already pointed out, probably every patient who receives arsphenamine intravenously gets some amount of the drug, small though it may be, in the cutis or in the subcutis. It therefore seems to me that when an arsphenamine dermatitis develops after a gross paravenous deposition of the drug this is a fortuitous association of events. The development of the sensitization depends on the person who is a candidate for the development of the dermatosis.

DR. LOUIS CHARGIN: I believe that Dr. Rostenberg Jr.'s view is entirely correct. Thousands of injections of arsphenamine are given intramuscularly, yet arsphenamine dermatitis develops in few patients. Why, then, should one stress paravenous infiltration as a special source of arsphenamine dermatitis? The mode of sensitization depends not on the paravenous infiltration but rather on the person to whom that treatment is given.

DR. SAMUEL FELDMAN: I certainly agree with the opinions expressed, that persons who become sensitive have something in their constitution which makes them so. An illustration of this is the fact that all persons come in contact with dust, yet few become sensitized. It is quite natural to expect that. However, when one observes an eruption in two of four patients who received paravenous infiltrations, one is bound to associate the two factors. The introduction of arsphenamine into the cutis is apparently one of the methods of sensitizing some patients to arsphenamine.

**Lichen Planus Zosteriformis.** Presented by DR. ARTHUR SAYER.

B. L., a woman aged 48, born in Rumania, presented herself on Feb. 23, 1937, at the Morrisania City Hospital on account of an itching eruption on the right lower extremity. The eruption had been present for the past four months.

The lesions are confined to the right lower extremity; they are arranged in linear bands which vary from 1 to 2 inches (2.5 to 5 cm.) in width and are distributed vertically from about the middle of the posterior aspect of the right thigh down to the achilles tendon. The lesions are most numerous on the lower half of the right leg and consist of erythematous maculopapules which tend to coalesce and in some areas show heaped-up grayish scales. Some of the lesions are definitely small papules, being the size of pinheads, with shiny tops and polygonal outlines; some have also a violaceous tint. The patient complains of severe itching in the involved region. There are three small papules on the flexor aspect of the left wrist and a single papule on the dorsum of the left hand. These papules are characteristic of lichen planus, since they are polygonal, flat topped, shiny and umbilicated. They are also extremly itchy.

Examination of the blood and urine gave negative results. The patient refused to submit to removal of tissue for biopsy.

DISCUSSION

DR. DAVID BLOOM: I suggest the diagnosis of linear dermatitis.

DR. PAUL GROSS: If the differential diagnosis between lichen planus and lichen simplex cannot be made on the basis of histologic examination, the response

to treatment with tar would decide in favor of lichen simplex, especially if it is combined with obliteration of the varicose veins.

**Lupoid Sycosis.** Presented by DR. DAVID BLOOM.

J. K., a man aged 25, presents a pustular follicular eruption of the bearded region. The outer portions of the eyebrows show partial alopecia. A plaque of alopecia and atrophic scarring is seen on both temples somewhat anteriorly to the ear.

The eruption began eight years ago with alopecia of the lateral portion of the eyebrows and has extended since then. The sycosis of the bearded region improved after application of an ointment containing sulfur and chlorhydroxyquinoline and a few injections of a staphylococcus vaccine.

DISCUSSION

DR. ARTHUR SAYER: There is no question about the diagnosis of sycosis of the face. However, the area which is located on the temples and is said to have existed since childhood shows considerable atrophy and telangiectasia. I am tempted to suggest that this is a radiodermatitis which followed roentgen treatment to the scalp given during childhood for some unknown disease. The lesions in this patient are too smooth and glistening and are not characteristic of lupoid sycosis.

DR. CHARLES WOLF: If Dr. Bloom has in mind a condition called ulerythema sycosiforme, it seems to me that the patient's eruption lacks some characteristics of that disease. Patients with ulerythema sycosiforme show advancing borders of pustules and areas of atrophy. This patient shows none of these sequelae. He may have a simple folliculitis of the bearded region.

DR. DAVID BLOOM: Physicians who have not observed many cases of this condition are prone to diagnose it as radiodermatitis. This patient has never received any roentgen treatment for the sycosis. I am sure that his assertion that the alopecia was present as long as he can remember is incorrect. I prefer the name of folliculitis sycosiformis atrophicans, given by Hoffmann, to that of lupoid sycosis, given by Brock. Hoffmann added the word capillitii, barbae or corporis, according to the location of the alopecia. The location on the temporal region is frequent. I assume that if the folliculitis which is seen surrounding the alopecia is not treated, the alopecia may spread so that finally it will surround the scalp in an ophiasis-like manner. The folliculitis in this patient has improved considerably as a result of application of an ointment containing sulfur and chlorhyroxyquinoline.

**Folliculitis Decalvans.** Presented by DR. SAMUEL FELDMAN.

J. P., a sign painter aged 28, states that he has noticed gradual thinning of the hair of the scalp for the past three years. In the past six months there has been intense itching of the scalp, for which he used a proprietary tonic (kreml). About two months ago he noticed bald patches on the scalp. Examination at that time showed in the occipital region a number of patches, the size of a dime or larger. The patches were completely devoid of hair, slightly depressed, reddish or pink and were surrounded by minute follicular pustules and papules. There was considerable itching.

The patient was given a 5 per cent ointment of ammoniated mercury to be applied once a day, and the papulopustular lesions cleared up within two weeks. Since then the lesions have become gradually paler. Now there is only a slight reddish surface visible.

The Wassermann reaction of the blood was negative.

## MINNESOTA DERMATOLOGICAL SOCIETY

DR. JOHN F. MADDEN, *President*

*Feb. 6, 1937*

DR. F. W. LYNCH, *Secretary*

**Hereditary Hemorrhagic Telangiectasia.** Presented by DR. JOHN F. MADDEN, St. Paul.

J. B., a laborer aged 56, states that telangiectases first appeared on the face about thirty years ago. New lesions have appeared at intervals; old lesions have enlarged, but none has disappeared. At present the skin of the face, of the neck and of the upper part of the trunk and the mucous membranes of the mouth and nasal septum are involved. There are also telangiectases in the conjunctiva. The patient has had nosebleeds as often as two or three times a day since childhood. In 1929 he was treated for what was thought to be a hemorrhagic duodenal ulcer. The patient's father has had repeated nosebleeds throughout his life. Studies of the blood, including determination of the bleeding time and clotting time, fragility tests and a platelet count, gave results which were within normal limits.

**A Case for Diagnosis (Trichotillomania?).** Presented by DR. JOHN F. MADDEN, St. Paul.

M. L., a girl aged 4 years, began to lose the hair from the crown of the head some time in October 1936. She has been a patient at the Gillette State Hospital for Crippled Children since June 1936 because of a congenital dislocation of the hip. The nurses emphatically state that she does not pull her hair or rub her head on the bed clothes. There has never been any eruption on the scalp, and the skin appears normal. On the crown of the head there is an area about the size of a large orange over which the hair is broken and partially lost. There is no apparent abnormality in the hair itself. Fungi could not be seen on microscopic examination.

DISCUSSION

DR. C. D. FREEMAN, St. Paul: I do not believe that this is a case of trichotillomania. There is a general thinning of the hair of the scalp. The hair that remains is all of the same length and does not in any way look as though it has been mechanically disturbed. The condition may be due to some endocrine disturbance.

**Malignant Melanoma.** Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. D. M., a housewife aged 24, states that a dime-sized flat black mole has been present on the middle portion of the extensor surface of the left arm since birth. As far as she knows, she has never injured the lesion. She became pregnant in August 1936. About Dec. 1, 1936, she noticed that the mole was elevated. It grew rapidly; at present it is the size of a large walnut. Satellite lesions varying in size from that of a pinhead to that of a large pea began to appear about Jan. 1, 1937. On Feb. 1, 1937, there were four or five hard, discrete, painless, palpable axillary lymph glands. Microscopic sections from the original growth and from one of the satellite lesions are shown.

DISCUSSION

DR. CARL LAYMON, Minneapolis: It would be wise to send this patient to the cancer institute at the university, since the outlook is extremely unfavorable. I think, however, that the treatment should consist of wide excision of the local lesion plus removal of the regional lymph nodes rather than of irradiation, since malignant melanoma is radioresistant in the majority of cases.

DR. F. W. LYNCH, St. Paul: I believe this patient should receive treatment regardless of the prognosis, if only to prevent the distress which will result from subsequent growth of the primary lesion. If I had an infiltrating lesion of this nature, I should be willing to subject myself to complete amputation of the arm at the shoulder joint and wide dissection of the axillary nodes. Dissection of the lesion alone and treatment of the nodes will not destroy any mole cells which may be in transit through the deep lymphatics of the upper portion of the arm, and these may lead to recurrence.

**Acute Disseminated Lupus Erythematosus.** Presented by DR. JOHN F. MADDEN, St. Paul.

**Papulonecrotic Tuberculid Involving the Leg and Foot.** Presented by DR. JOHN F. MADDEN, St. Paul.

**Lichen Planus.** Presented by DR. J. F. MADDEN, St. Paul.

Miss D. B., a student nurse aged 18, states that two asymptomatic orange-red lesions appeared on the medial surface of the left thigh just above the knee in January 1936. The lesions spread and formed irregular plaques, and independent small papules appeared between these larger plaques. The patient states that none of the old lesions has disappeared. The eruption now covers the medial surface of the distal third of the thigh. The primary lesion is a flat orange to bright red papule covered with a fine scale. The rest of the cutaneous surface shows no sign of an eruption.

Biopsy showed typical purpuric pigmented lichenoid dermatitis.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I think the condition is pigmented purpuric lichenoid dermatitis, although one would have to see the section before completely eliminating lichen planus as a possibility.

DR. C. D. FREEMAN, St. Paul: I cannot make a positive diagnosis, but I do not believe that the condition is lichen planus, as there is not one papule characteristic of lichen planus. The eruption has a peculiar xanthomatous hue.

**Neurodermatitis.** Presented by DR. JOHN F. MADDEN, St. Paul.

L. B., a Jew aged 33, states that he has had a more or less generalized dermatitis since his early childhood. The eruption has always been more marked on the face, neck and groin and in the antecubital and popliteal spaces. There are now weeping lichenified, crusted patches in these areas. The patient has been in the hospital off and on during the past ten years, when the eruption became generalized and more acute. The scalp and the hairy parts of the body have always been free. The patient and his family have noticed that the eruption is worse whenever he is under a mental strain. The father has asthma and atopic eczema. General examination gave negative results except for controlled syphilis of the central nervous system. Fungi were not observed in scrapings from the lesions. Scratch tests, patch tests, elimination diets, change of environment and many types of internal and external medication have not altered the eruption for any length of time.

DISCUSSION

DR. ELMER M. RUSTEN, Minneapolis: The eruption involves areas generally affected by seborrhea. The lesions conform to those seen in neurodermatitis. It appears that atopic diseases are often encountered in patients with this type of disease.

DR. JOHN F. MADDEN, St. Paul: Seborrheic eczema, regardless of its extent, usually responds to one of the common remedies recommended for it. This

patient's eruption does not seem to be influenced a great deal by any medication. Infection follows scratching and appears to be secondary.

DR. CARL LAYMON, Minneapolis: This patient presents postauricular changes which coincide with Mitchell's description of streptococcic dermatitis. Sabouraud has given the name streptococcic eczematid to this type of condition.

DR. RICHARD J. BAILEY, Rochester, Minn.: This case demonstrates the need of further study of the conditions grouped under the classification of seborrheic eczema. There seems to be a somewhat greater incidence of the severe refractive intertriginous involvement in members of the Jewish race. The rôle of Monilia in this type of eruption has been stressed by some, but one must carefully determine whether or not the organism is a pathogen, as it can be cultured from nearly every normal groin. The pertinence of the atopic, seasonal and family history in this case must also be carefully determined.

**Atopic Dermatitis. Cataract of the Left Eye. Chorioretinitis of the Right Eye.** Presented by DR. JOHN F. MADDEN, St. Paul.

F. A., an unemployed man aged 27, states that a generalized eruption appeared in 1923 and has never entirely disappeared since. The eruption was more marked on the face, neck, antecubital and popliteal spaces but at times became generalized. The skin in the involved areas is now leathery, lichenified, deeply pigmented and excoriated and shows many scars. During the acute stage the eruption weeps and becomes crusted; the primary lesion is an inflammatory papulovesicle, which becomes pustular. The patient has noticed that the eruption is always worse in the winter. He had an acute attack in the summer of 1935, when he removed wallpaper from the walls of a room and painted them. He also experienced a severe exacerbation in November 1936, shortly before he was to be best man at a wedding. He states that his vision is always worse when the eruption is at its height.

The patient has always had poor vision in the right eye. Vision began to fail in the left eye in 1932. Shortly after he noticed the impairment examination showed a cataract of the left eye and detachment of the retina and chorioretinitis in the right eye.

Laboratory examinations, including a Mantoux test and a Wassermann examination of the blood gave negative results. Scratch tests and patch tests revealed nothing of importance except a marked reaction to turpentine. There is no history of allergic disease in the family.

DISCUSSION

DR. RICHARD J. BAILEY, Rochester, Minn.: There seems to be a definite tendency toward pigmentation of the face, neck and upper portion of the chest in this condition, which is not dependent on the amount of roentgen or ultraviolet radiation alone but consists of a residual change in the lichenified areas. The occurrence of cataract in association with atopic dermatitis is observed in too large a number of cases to be considered incidental.

**Primary Tuberculous Complex.** Presented by DR. JOHN F. MADDEN, St. Paul.

J. M., a Mexican boy aged 9 years, was presented at a meeting of this society in October (ARCH. DERMAT. & SYPH. **35**:1181 [June] 1937). At that time the diagnoses of pyoderma and scrofuloderma were considered, and Dr. H. E. Michelson made the diagnosis of primary tuberculous complex.

The information obtained since the last presentation is as follows: Mantoux tests were negative until December 12. Since then the reaction has been positive to an increasing degree. A guinea-pig inoculated with material from the lesion showed tuberculosis and died. The patient now has a daily afternoon rise of temperature to about 100 F. Roentgenograms of the chest and mandible showed no abnormalities. The cervical glands began to break down about Jan. 10, 1937, and pus has been aspirated at regular intervals since that time.

Microscopic sections were shown.

**A Case for Diagnosis (Variola? Varicella? Reticulo-Endotheliosis?).** Presented by Dr. J. F. Madden, St. Paul.

P. H., a laborer aged 25, states that ten days ago he had sore throat, headache, backache and muscular pains. In the next day or two a sparse, generalized eruption appeared. New lesions continued to appear during the entire ten days. The eruption is multiform, and lesions are irregularly scattered over the cutaneous surface. There is one pea-sized inflammatory vesicle on the hard palate. Most of the lesions are firm bluish red inflammatory papules from the size of a pea to that of a dime, capped by grouped pinhead-sized vesicopustules or crusts. There are deep-seated vesicopustular lesions on the palms and soles. There are also firm warm and slightly painful deep-seated bluish red papules and nodules from the size of a bean to that of a split olive scattered over the upper extremities. The patient seems ill and has a temperature of 102 F.

Note.—The temperature receded slowly over a five day period. No new lesions appeared. Physical examination gave negative results. Biopsy showed destructive deep-seated vesicopustular lesions characteristic of variola.

DISCUSSION

Dr. H. E. Michelson, Minneapolis: My diagnosis is either chickenpox or atypical smallpox. I definitely think that the condition is an acute exanthem. I think that the acute onset, the pustular type of lesion, the high fever and the pains in the back point more to smallpox. The presence of palmar, plantar and palatine lesions should also be noted.

Dr. Elmer M. Rusten, Minneapolis: I believe this patient has an acute exanthem. The diagnosis of generalized herpes zoster should be considered.

Dr. Carl Laymon, Minneapolis: In this type of dermatosis it is not always possible to make a diagnosis after only one examination. Continued observation will perhaps make a decision possible. Although it seems from the clinical features that the most likely diagnosis is hemorrhagic varicella, the final opinion should be reserved until further studies, such as biopsy and examination of the blood, have been made.

Dr. C. D. Freeman, St. Paul: On first examination I thought that the condition was dermatitis medicamentosa. I agree with Dr. Michelson that it probably is atypical smallpox.

Dr. F. W. Lynch, St. Paul: The lesions are quite superficial and appear to be epithelial. These are points which should differentiate the eruption from that of reticulo-endotheliosis in which the pathologic process lies deep in the cutis. I favor a diagnosis of varicella. That disease frequently runs a severe and atypical course in adults. Both clinical and histologic differentiation from variola is difficult.

**Generalized Telangiectasia of Undetermined Etiology (Angioma Serpiginosum?).** Presented by Dr. H. E. Michelson, Minneapolis, and Dr. John F. Madden, St. Paul.

M. L., a woman, aged 39, has had the present eruption for from ten to eleven years. She first noticed a red spot on the left arm; later similar lesions appeared on the other arm, on the trunk and on the legs. The eruption covered most of the extremities but was more marked on the thighs and legs. The primary lesions were telangiectatic macules of various sizes which enlarged peripherally. Some of the lesions took on the appearance of spider nevi. The entire eruption was asymptomatic. The patient had rheumatism in 1922 and jaundice in 1936. She has taken no drugs at any time. Thorough general examination, including search for foci in the nose, throat, teeth and pelvis, gave negative results.

Laboratory examination, including a complete examination of the blood, a Wassermann test, and a Mantoux test, gave negative results. Biopsy showed only diffuse telangiectasia.

DISCUSSION

DR. CARL LAYMON, Minneapolis: This is a classic example of Osler's hereditary telangiectasia. Angioma serpiginosum has always seemed to me to be a rather vague entity. The generalized telangiectasia exhibited by this patient in many respects fits the description of that disease, although there is no visible atrophy. The latter feature, however, is not a requisite for the diagnosis of angioma serpiginosum. If pigmentation and atrophy were present in addition to the telangiectasia it would be necessary to consider a diagnosis of poikiloderma of Jacobi. Extensive studies made at the University Hospitals disclosed no etiologic factors for the condition.

DR. RICHARD J. BAILEY, Rochester, Minn.: I note that in this case angioma serpiginosum was considered in the differential diagnosis. While I reviewed the literature in preparation for the case report published by Dr. Hamilton Montgomery and me (*Brit. J. Dermat.* **47**:456-463 [Nov.] 1935) I noted that there was repeated mention of several clinical characteristics not present in this case. The primary lesion seems to be a bright to copper red punctum with a papular tendency which does not fade materially on pressure with the diascope. The circinate or serpiginous outline results from the formation of new puncta in such an arrangement. Progression and regression are constant, and there are interspersed active and clearing areas. I feel strongly, as does Dr. Madden, that the condition in this case should be grouped with the generalized telangiectasias (angiomatosis), since the primary lesion is a dilated vessel which completely disappears on pressure with the diascope. Histologically, only dilated vessels were observed, while in angioma serpiginosum varying amounts of a predominantly lymphocytic infiltrate are present in the upper portion of the cutis and there is some degree of liquefaction necrosis of the basal cell layer in addition to the dilated and newly formed blood vessels.

DR. JOHN F. MADDEN, St. Paul: I do not think that the condition is like that reported by Wise or Montgomery. There is not, and there never has been, any evidence of inflammation or atrophy. Inflammatory change present at one time or another was one of the outstanding features in the case of Wise and in that of Montgomery.

**A Case for Diagnosis (Acne Varioliformis? Seborrheic Eczema?).** Presented by DR. S. E. SWEITZER and DR. L. H. WINER, Minneapolis.

# Book Reviews

**Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes: Manifestations, Diagnosis and Treatment.** By Albert H. Rowe, M.S., M.D. Cloth. Price. $8.50. Pp. 812. Philadelphia: Lea & Febiger, 1937.

This book is more comprehensive than the author's previous work on food allergy. It embraces the entire field of clinical allergy due to foods, inhalants, contact substances, drugs, physical agents and bacteria. Symptoms and diseases of almost every part of the body, including the skin, the respiratory system, the eyes, the gastro-intestinal tract, the joints, the genito-urinary system and the nervous system, are considered from the standpoint of allergic manifestations.

Throughout the volume the author stresses the importance of food allergy in the production of symptoms. He finds "elimination diets" much more practical and satisfactory than cutaneous tests in the diagnosis of food allergies. He goes into detail in describing the "elmination diets" that he has developed and includes menus for adults and children of various ages in chapter 4; other menus for diets of various types are included in the appendix. Detailed directions for the proper preparation of foods will be found valuable.

Of special interest to dermatologists is a chapter of 80 pages devoted to allergic dermatoses. Under this heading the author includes eczema, urticaria, papular urticaria, prurigo mitis, angioneurotic (localized) edema, generalized edema, erythematous types of cutaneous lesions, acne, canker and recurrent herpetic lesions and in certain cases psoriasis, rosacea, pruritus ani and lupus erythematosus. As in other diseases, the author ascribes to food allergy a prominent rôle in the etiology of most of the conditions named—a conclusion with which dermatologists generally will not agree. The author is inclined to draw definite conclusions on the basis of meager evidence and too frequently on the basis of occasional instances.

Specialists in other branches of medicine may also take exception to some of the author's views. For example, neurologists and psychiatrists may differ with the following statement, on page 47: "Allergy especially is responsible for much body consciousness making patients introspective, self-centered, and preventing the proper utilization of their physical and mental powers and satisfactory integration of emotional and intellectual resources. It is possible that the failure of recognition of food and other types of sensitization explains in part why Sir James Mackenzie was unable to make a satisfactory diagnosis in three out of four of his patients."

A curious error is found on page 21, where the statement is made: "In this volume antibody will be used as synonymous with allergen." Obviously, allergen, which is another name for antigen, cannot be the same as antibody. On the bottom of page 361 is a misprint of two extra lines.

All in all, the book is an interesting addition to the existing works on allergy and will be found useful to the general practitioner, although experts may differ with some of the author's contentions.

# Directory of Dermatologic Societies *

## INTERNATIONAL

NINTH INTERNATIONAL CONGRESS OF DERMATOLOGY AND SYPHILOLOGY

American Secretary: Dr. Howard Fox, 140 E. 54th St., New York.

## FOREIGN

BRITISH ASSOCIATION OF DERMATOLOGY AND SYPHILOLOGY
(CANADIAN BRANCH)

J. J. McGovern, President, 4005 Dorchester St., Montreal.
F. L. Boulais, Secretary-Treasurer, 2061 St. Denis St., Montreal.

ROYAL SOCIETY OF MEDICINE, SECTION OF DERMATOLOGY

H. W. Barber, President, 7 Devonshire Pl., London, W. 1.
Louis Forman, Secretary, 7 Devonshire Pl., London, W. 1.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Joseph V. Klauder, Chairman, 1934 Spruce St., Philadelphia.
J. Bedford Shelmire, Secretary, 1719 Pacific Ave., Dallas, Texas.
Place: San Francisco. Time: June 13-17, 1938.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

Howard Fox, President, 140 E. 54th St., New York
C. Guy Lane, Secretary, 416 Marlborough St., Boston.
Place: San Francisco. Time: June 1938.

AMERICAN DERMATOLOGICAL ASSOCIATION

James Herbert Mitchell, President, 25 E. Washington St., Chicago.
Fred D. Weidman, Secretary, University of Pennsylvania, Philadelphia.
Place: Del Monte, Calif. Time: June 8-11, 1938.

## SECTIONAL

CENTRAL STATES DERMATOLOGICAL ASSOCIATION

George H. Belote, President, University Hospital, Ann Arbor, Mich.
Thomas H. Miller, Secretary-Treasurer, 1305 David Whitney Bldg., Detroit.
Place: Detroit. Time: December 1937.

MISSISSIPPI VALLEY DERMATOLOGICAL SOCIETY

A. H. Conrad, President, 3720 Washington Blvd., St. Louis.
Roy L. Kile, Secretary-Treasurer, 3720 Washington Blvd., St. Louis.
Place: St. Louis, Mo. Time: Dec. 4, 1937.

NEW ENGLAND DERMATOLOGICAL SOCIETY

Fred S. Burns, President, 83 Marlborough St., Boston.
B. Appel, Secretary, 483 Beacon St., Boston.

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* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

NORTHERN NEW JERSEY DERMATOLOGICAL SOCIETY

Charles R. Mitchell, President, 311 Broadway, Paterson.
Louis J. B. LeBel, Secretary, 165 Grant Ave., Nutley.
Place: Academy of Medicine of Northern New Jersey, Newark. Time: Third Tuesday of March, April, October and December.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Harry M. Robinson, Chairman, 106 E. Chase St., Baltimore, Md.
Winston U. Rutledge, Secretary, 332 W. Broadway, Louisville, Ky.
Place: New Orleans. Time: Nov. 30-Dec. 1-3, 1937.

## STATE

CALIFORNIA MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, DERMATOLOGY AND SYPHILOLOGY SECTION

Stanley O. Chambers, Chairman, 727 W. 7th St., Los Angeles.
Nelson Paul Anderson, Secretary, 2007 Wilshire Blvd., Los Angeles.
Place: Pasadena. Time: May 9-12, 1938.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY

E. Myles Standish, Chairman, 179 Allyn St., Hartford.
Albert Levenson, Secretary, 881 Lafayette St., Bridgeport.
Place: New Haven. Time: May 19, 1938.

FLORIDA SOCIETY OF DERMATOLOGY AND SYPHILOLOGY

C. A. Andrews, Chairman, 706 Franklin St., Tampa.
Lauren Sompayrac, Secretary, 204 Laura St., Jacksonville.
Place: Jacksonville. Time: June 1938.

LOUISIANA DERMATOLOGICAL SOCIETY

M. T. Van Studdiford, President, 912 Pere Marquette Bldg., New Orleans.
R. A. Oriol, Secretary-Treasurer, 921 Canal St., New Orleans.

MASSACHUSETTS MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

George A. Dix, President, 6 Ashland St., Worcester.
J. Harper Blaisdell, Secretary, 45 Bay State Rd., Boston.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Leo Spiegel, Chairman, 241 W. 100th St., New York.
Mark Heiman, Secretary, 600 Medical Arts Bldg., Syracuse.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA SECTION ON DERMATOLOGY

Frederick M. Jacob, Chairman, Jenkins Arcade Bldg., Pittsburgh.
L. G. Beinhauer, Secretary, 5026 Jenkins Arcade Bldg., Pittsburgh.

MICHIGAN STATE MEDICAL SOCIETY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

G. Warren Hyde, Chairman, 2501 W. Grand Blvd., Detroit.
Ruth Herrick, Secretary, 26 Sheldon Ave., Grand Rapids.
Place: Grand Rapids. Time: Sept. 27-30, 1937.

### Minnesota Dermatological Society

John Madden, President, 350 St. Peter St., St. Paul.
F. W. Lynch, Secretary-Treasurer, Lowry Medical Arts Bldg., St. Paul.
Time: First Friday in October, December, February and April.

### Oklahoma State Dermatological Society

Charles P. Bondurant, President, 412 Medical Arts Bldg., Oklahoma City.
Darrell G. Duncan, Secretary, 914 Medical Arts Bldg., Oklahoma City.

### Texas Dermatological Society

Bedford Shelmire, President, 1719 Pacific Ave., Dallas.
Everett R. Seale, Secretary, 1215 Walker Ave., Houston.
Place: Galveston. Time: May 9-12, 1938.

## LOCAL

### Baltimore-Washington Dermatological Society

Leon Ginsburg, President, The Walbert, Baltimore.
Francis A. Ellis, Secretary, 104 W. Madison St., Baltimore.
Place: Baltimore. Time: October 1937.

### Bronx Dermatological Society

Theodore Rosenthal, Chairman, 115 W. 86th St., New York.
Henry Silver, Secretary, 290 West End Ave., New York.
Time: June 1938.

### Brooklyn Dermatological Society

David L. Satenstein, President, 57 W. 57th St., New York.
M. Edward Goebel, Secretary, 842 Union St., Brooklyn.
Time: Third Monday of each month except June, July, August and September.

### Buffalo-Rochester Dermatological Society

I. J. Arnsson, President, 468 Delaware Ave., Buffalo.
Richard L. Saunders, Secretary, 333 Linwood Ave., Buffalo.
Place: Buffalo. Time: Jan. 11, 1938.

### Central New York Dermatological Society

Mark Heiman, President, 713 E. Genesee St., Syracuse.
Rudolph Ruedemann Jr., Secretary-Treasurer, 256 State St., Albany.

### Chicago Dermatological Society

Otto H. Foerster, President, 208 N. Wisconsin Ave., Milwaukee.
Herbert Rattner, Secretary, 25 E. Washington St., Chicago.
Place: Chicago. Time: Third Wednesday in January 1938.

### Cincinnati Dermatological Society

Leon Goldman, President, Doctors Bldg., Cincinnati.
George E. Clarke, Secretary-Treasurer, 19 W. 7th St., Cincinnati.
Place: Detroit.

### Cleveland Dermatological Society

Claude B. Norris, President, 244 Lincoln Ave., Youngstown, Ohio.
Clyde L. Cummer, Secretary, 1010 Hanna Bldg., Cleveland.
Place: Cleveland. Time: May 26, 1938.

### Detroit Dermatological Society

George H. Belote, President, University Hospital, Ann Arbor, Mich.
Thomas H. Miller, Secretary-Treasurer, 1305 David Whitney Bldg., Detroit.
Place: Detroit. Time: May 1938.

### Los Angeles Dermatological Society

Thomas W. Nisbet, President, 65 N. Madison Ave., Pasadena, Calif.
C. R. Caskey, Secretary, 1930 Wilshire Blvd., Los Angeles.
Time: Second Tuesday of each month, October to May, inclusive.

### Manhattan Dermatologic Society

Andrew J. Gilmour, Chairman, 121 E. 60th St., New York.
Anthony C. Cipollaro, Secretary, 40 E. 61st St., New York.
Place: New York. Time: May 1938.

### Montreal Dermatological Society

B. Usher, President, 1538 Sherbrooke St., W., Montreal, Canada.
Paul Poirier, Secretary, 450 Sherbrooke St., E., Montreal, Canada.

### New York Academy of Medicine, Section of Dermatology and Syphilis

Louis Chargin, Chairman, 1 W. 85th St., New York.
Harry C. Saunders, Secretary, 159 W. 87th St., New York.

### New York Dermatological Society

Eugene F. Traub, President, 140 E. 54th St., New York.
Frank C. Combes, Secretary, 80 W. 40th St., New York.

### Omaha Dermatological Society

Donald J. Wilson, President, 1113 Medical Arts Bldg., Omaha.
Leonard J. Owen, Secretary-Treasurer, 954 Stuart Bldg., Omaha.

### Philadelphia Dermatological Society

Frank C. Knowles, Chairman, 2035 Spruce St., Philadelphia.
Thomas Butterworth, Secretary, 411 Walnut St., Reading, Pa.
Time: Third Friday of each month from September to May, inclusive.

### Pittsburgh Dermatological Society

A. Fisher, President, 530½–5th Ave., McKeesport, Pa.
Francis P. Kenney, Secretary, Westinghouse Bldg., Pittsburgh.

### St. Louis Dermatological Society

A. H. Conrad, President, 3720 Washington Blvd., St. Louis.
Roy L. Kile, Secretary-Treasurer, 3720 Washington Blvd., St. Louis.
Place: Barnard Free Skin and Cancer Hospital. Time: 2 p. m., second Wednesday of each month.

### San Francisco Dermatological Society

John M. Graves, President, 909 Hyde St., San Francisco.
H. V. Allington, Secretary, 3115 Webster St., Oakland.
Place: San Francisco. Time: Third Friday of November 1937.